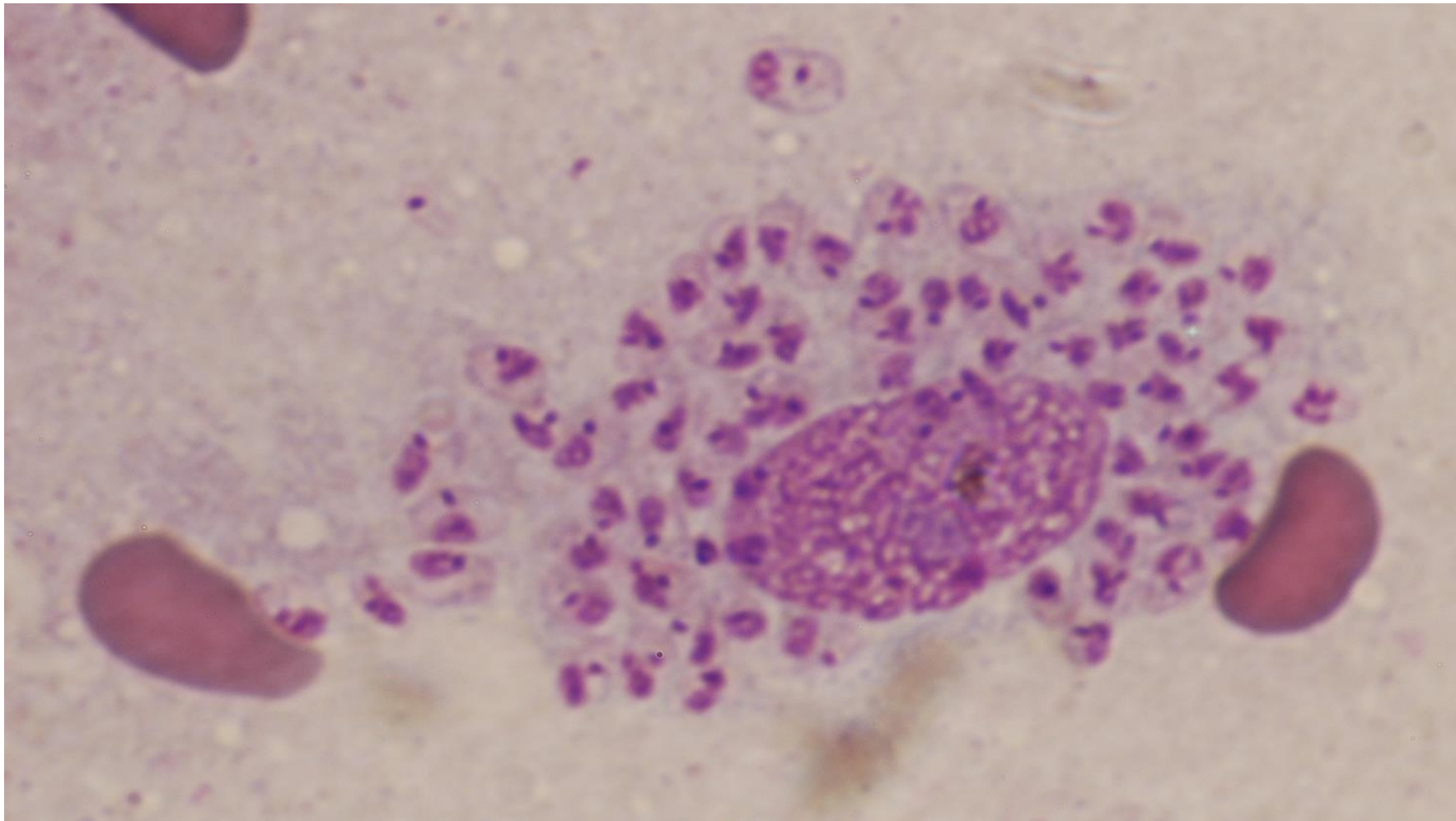
DIU **« Stratégies Thérapeutiques et Préventives en Pathologie Infectieuse »**

Leishmaniose

Mardi 13 Mars 2025



Pierre Buffet
Université Paris Cité, APHP
& Institut Pasteur, Paris

Leishmaniose Points clés

Viscérale

1. Maladie surtout européenne
2. PCR sang quantitative d'abord
3. **AmBisome 21 mg/kg cumulés**
4. Immunodéprimé 40-60 mg/kg cumulés et contrôler la charge (PCR négative) avant prophylaxie 2aire par AmBisome ou miltéfosine ou pentamidine ou antimoine ou paromomycine

L'Amphotéricine B liposomale
est formidable mais ne résout pas tout

Cutanée

1. **Lésion infiltrée prolongée inexpliquée au retour**
2. Qualité du prélèvement local
3. Bénéfice-risque difficile à déterminer car maladie rarement grave
4. Traitement local svt possible (crème paromomycine ou CryoSbIL*)
5. Association *L. infantum*
Immunodépression Atteinte muqueuse
AmBisome > 30 mg/kg cumulés

*CryoSbIL
= Cryothérapie et injections intra-lésionnelles de Glucantime

N'hésitez pas à appeler ou écrire : 06 26 16 68 11 pierre.buffet@pasteur.fr clea.melenotte@aphp.fr

CONSEIL THÉRAPEUTIQUE

Le traitement des leishmanioses reste complexe, en raison de la multiplicité des formes cliniques, de la variabilité de leur évolution et des différentes espèces de *Leishmania* impliquées.

Il est réservé au corps médical et est accessible par téléphone ou éventuellement par e-mail aux adresses suivantes

– Département de Parasitologie-Mycologie, CHRU de Montpellier

Dr Christophe Ravel, Pr. Laurence Lachaud
Tél. 04 67 33 23 50, **e-mail**

– Institut National de la Transfusion Sanguine & Centre d'Infectiologie Necker-Pasteur

Pr. Pierre Buffet
Tél. 06 26 16 68 11 / 01 44 49 31 13 , **e-mail**

N'hésitez pas à appeler ou écrire : 06 26 16 68 11
pierre.buffet@pasteur.fr clea.melenotte@aphp.fr

Un formulaire de demande d'avis thérapeutique à l'usage des praticiens pour la prise en charge des patients atteints de leishmaniose est disponible :

– Pour une leishmaniose cutanée	***– Pour une leishmaniose viscérale***

L'objectif est de proposer, soit en direct – soit pour les cas plus complexes dans les 48 heures – une option thérapeutique au cas par cas.

– Référentiel consensuel français 2011
Traitement des leishmanioses en France : proposition d'un référentiel consensuel. Presse Med. 2011;40:173-84

– Référentiel du groupe européen LeishMan 2014
LeishMan recommendations for treatment of cutaneous and mucosal leishmaniasis in travelers, 2014. Travel Med. 2014;21(2):116-29

– Référentiel de l'American Society of Tropical Medicine and Hygiene 2017
Diagnosis and Treatment of Leishmaniasis: Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). Am J Trop Med Hyg. 2017;96(1):24-45

Parasitologie & Epidémiologie

Classification simplifiée des principaux parasites & champignons du programme

Plantes (Plantae)

Organismes procaryotes
Bactéries

Virus

Organismes eucaryotes

Organismes multicellulaires (Métazoaires)

Vers (Helminthes) — Hyperéosinophilie

- Cylindriques — **Nématodes**
  - Intestinaux : Oxyures Ankylostomes Ascaris …. Anguillules
  - Tissulaires : Trichines *Toxocara sp.* — Larva migrans viscérale
  - Sanguins : Filaires
- Plats non segmentés — **Trématodes**
  - Douves — Distomatose
  - Schistosomes — Bilharziose
- Plats segmentés — **Cestodes**
  - *Taenia sp.*
  - *Echinococcus sp.* — Hydatidose

Acariens

Insectes

Protozoaires

Apicomplexes

- *Plasmodium sp.* — Paludisme
- *Toxoplasma gondii*
- Cryptosporidies

Amibes & ciliés

- *Entamoeba histolytica* — Diarrhée Abcès hépatique

Kinetoplastidés

- *Leishmania sp.*
- *Trypanosoma sp.* — Maladie du sommeil ; Maladie de Chagas

Protozoaires "rares"

- Microsporidies

Champignons

Levures	Filamenteux	Dimorphiques
Levures chez le patient Levures en culture	Filamenteux chez le patient Filamenteux en culture	Levures chez le patient Filamenteux en culture

Superficiel — Lésions cutanées
- *Candida albicans*
- *Candida sp.*
- Dermatophytes

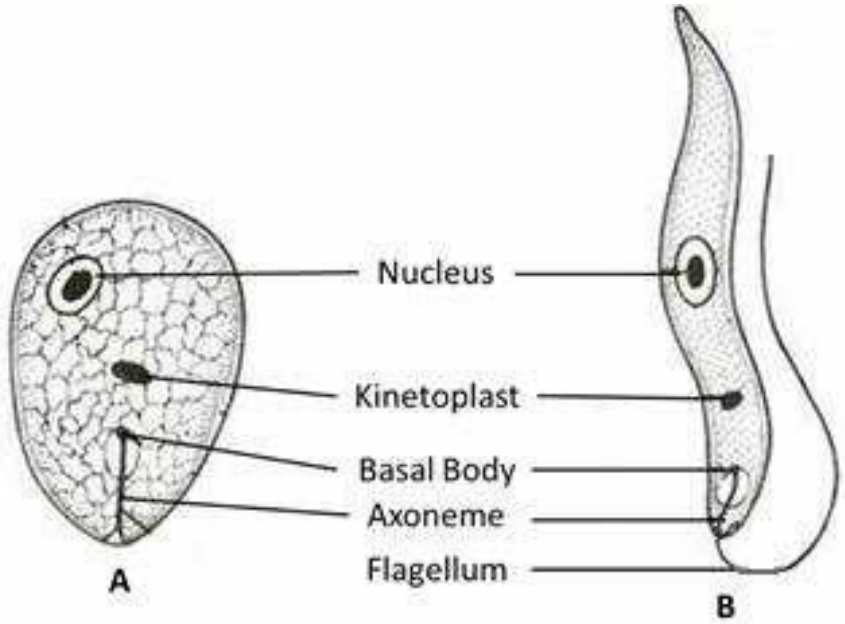
Profond — Infections systémiques sévères de l'immunodéprimé
- *Candida albicans*
- *Candida sp.*
- *Aspergillus fumigatus*
- *Aspergillus sp.*
- *Histoplasma capsulatum*
- Pneumopathie focale → *Cryptococcus neoformans*
- Pneumopathie diffuse → *Pneumocystis jiroveci*

Classification "officielle" des champignons
Ascomycètes (ascomycota) — Basidiomycètes (Basidiomycota)
Zygomycètes (Zygomycota) — Champignons "imparfaits" (Deutero mycota)

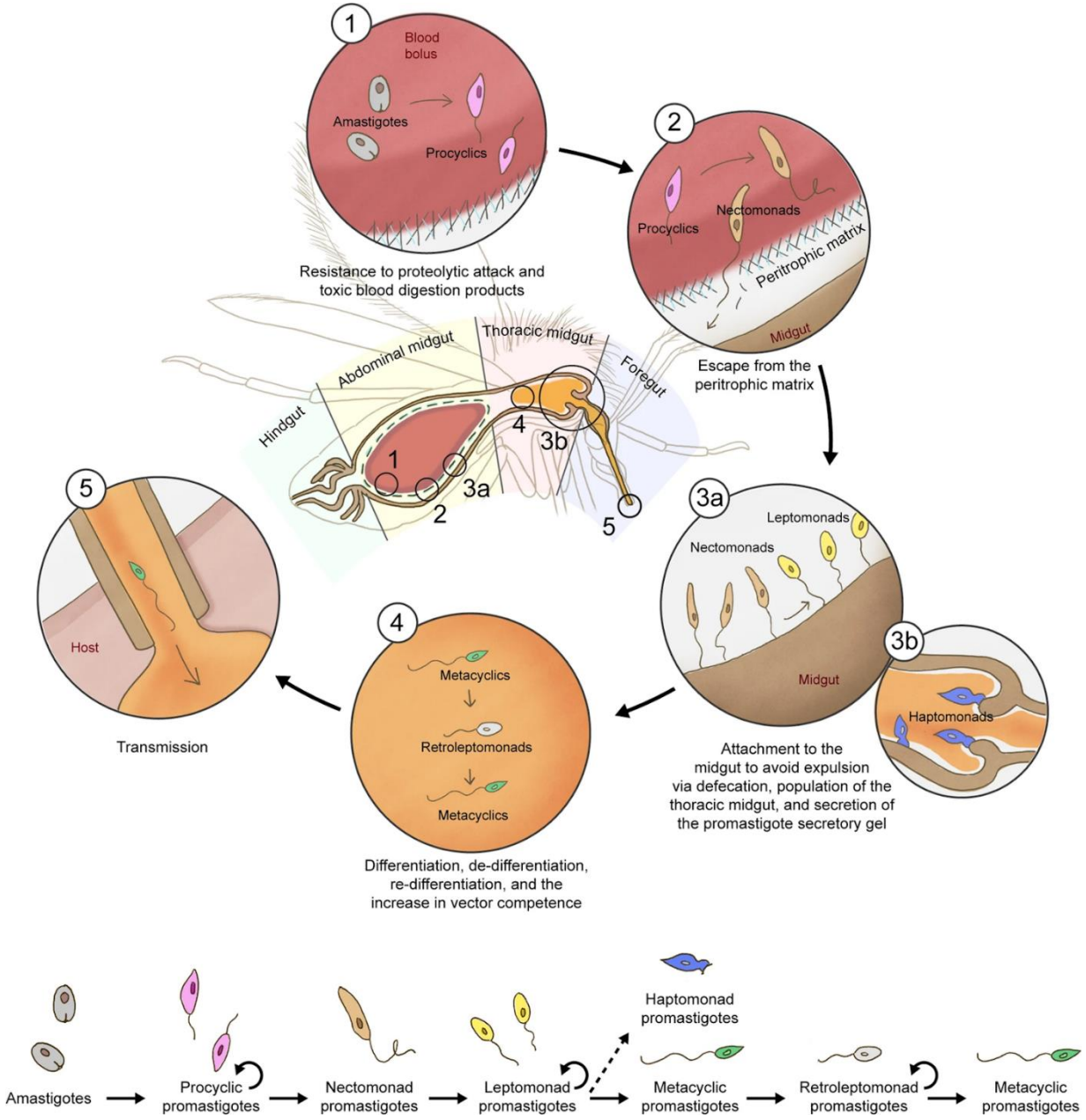
Promastigote mobile (phlébotome culture)

(Bates et Rogers, 2004) (Chappuis, F et al, 2007)

Transmission facilitée par :
- Bouchon de protéophosphoglycanes (PSG) :
→ Bloque le tube digestif du phlébotome, le forçant à régurgiter lors de la piqûre
- Endommagement valve stomodéale du phlébotome
→ Plusieurs piqûres/ hôtes pour se nourrir
- Protéines chemotactiques dans la salive du phlébotome favorisant des réponses immunitaires en attirant les neutrophiles (Cecilio et al, 2022)

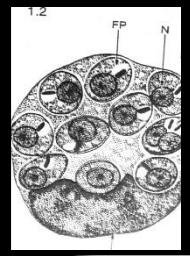


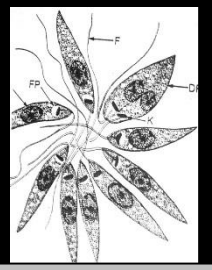
Morphological forms of Leishmania. (A) Amastigote, (B) Promastigote. (Manas Paramanik, 2023)



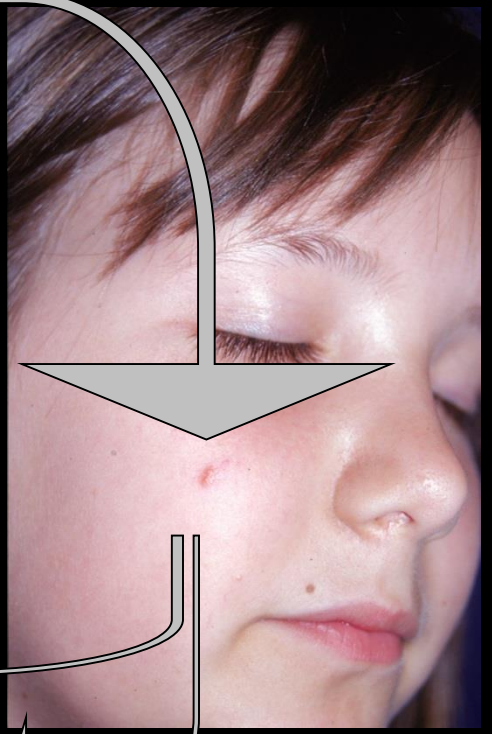
Leishmania development within the sand fly midgut (Cecilio et al, 2022)

Amastigotes

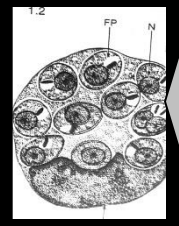




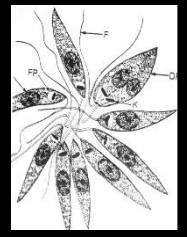
Promastigotes



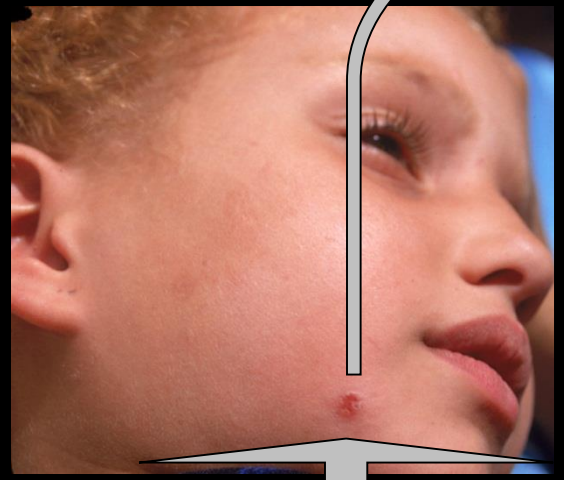
Smear or biopsy



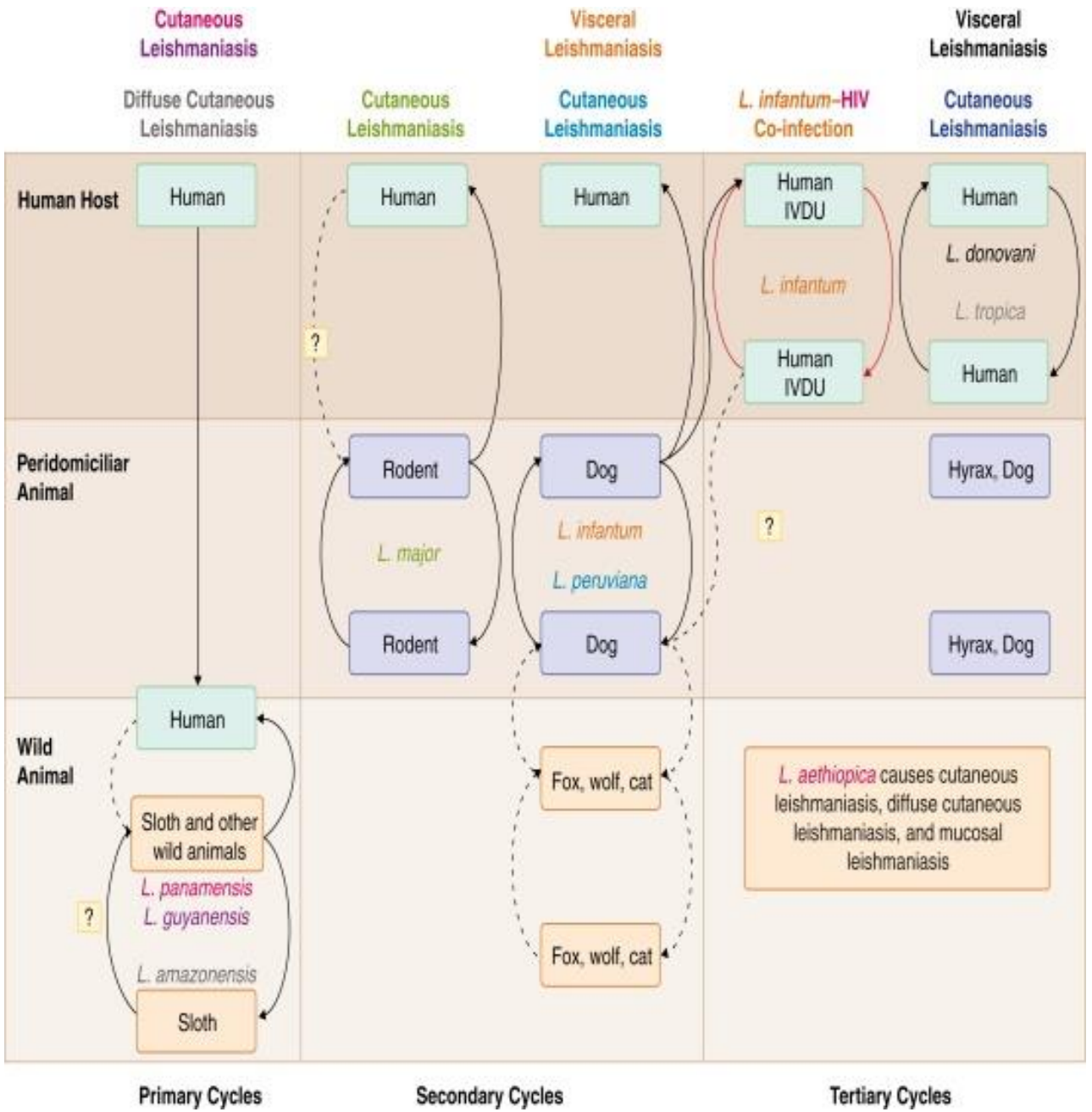
Culture



Identification



Cycle anthroponotique :
L. tropica



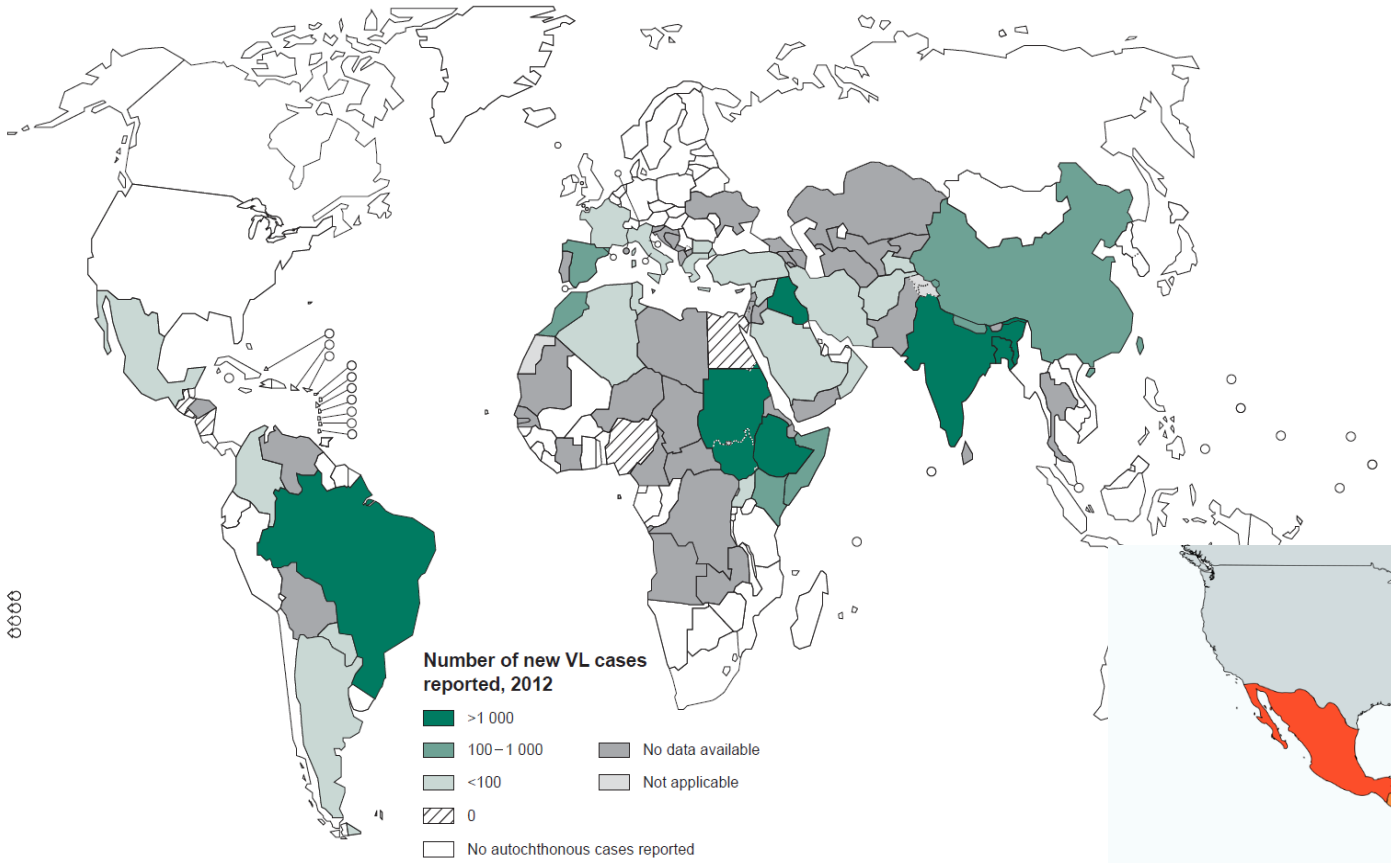
Risque d'émergence de résistance élevé

Risque d'émergence de résistance faible

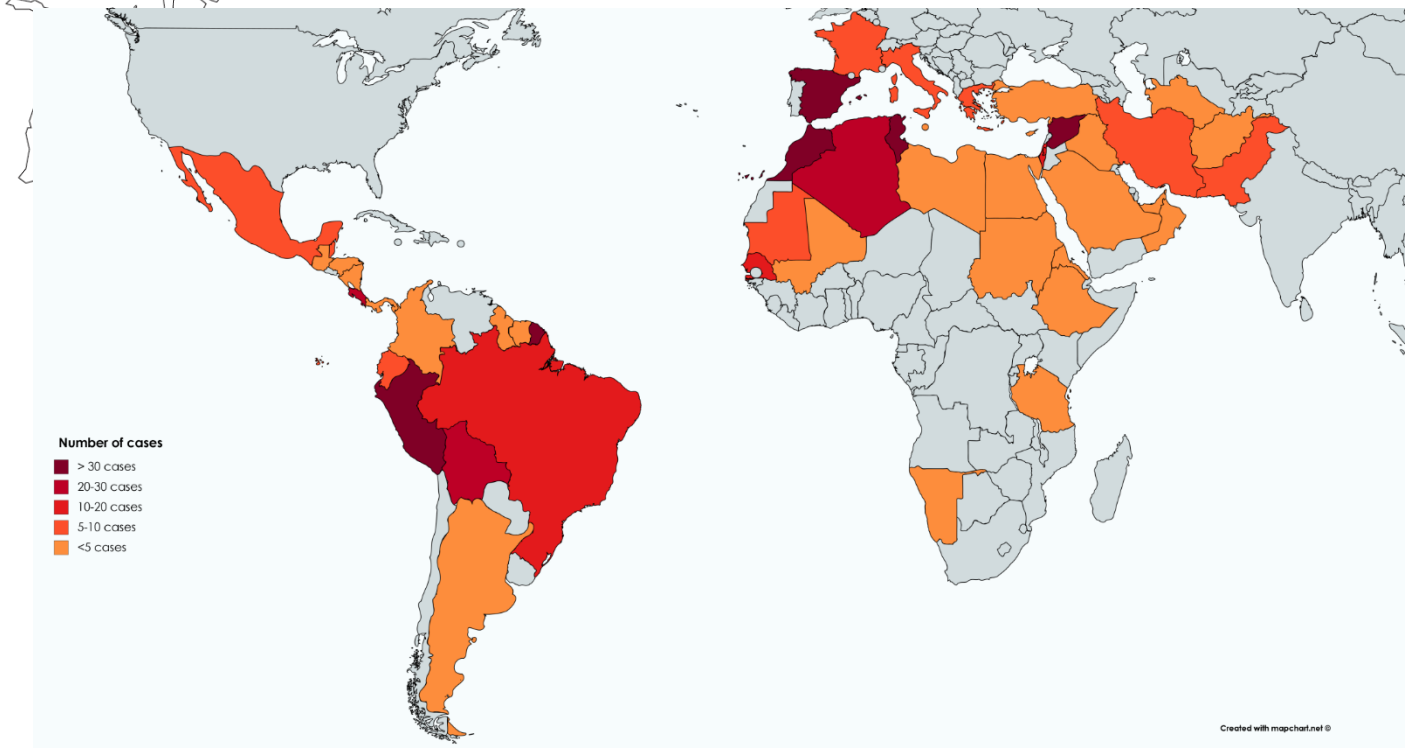
From Buffet, Croft and Chatterjee. Cecil's Internal Medicine textbook 2023

Fig. 4.9.1 Distribution of visceral leishmaniasis, worldwide, 2012

Viscérale

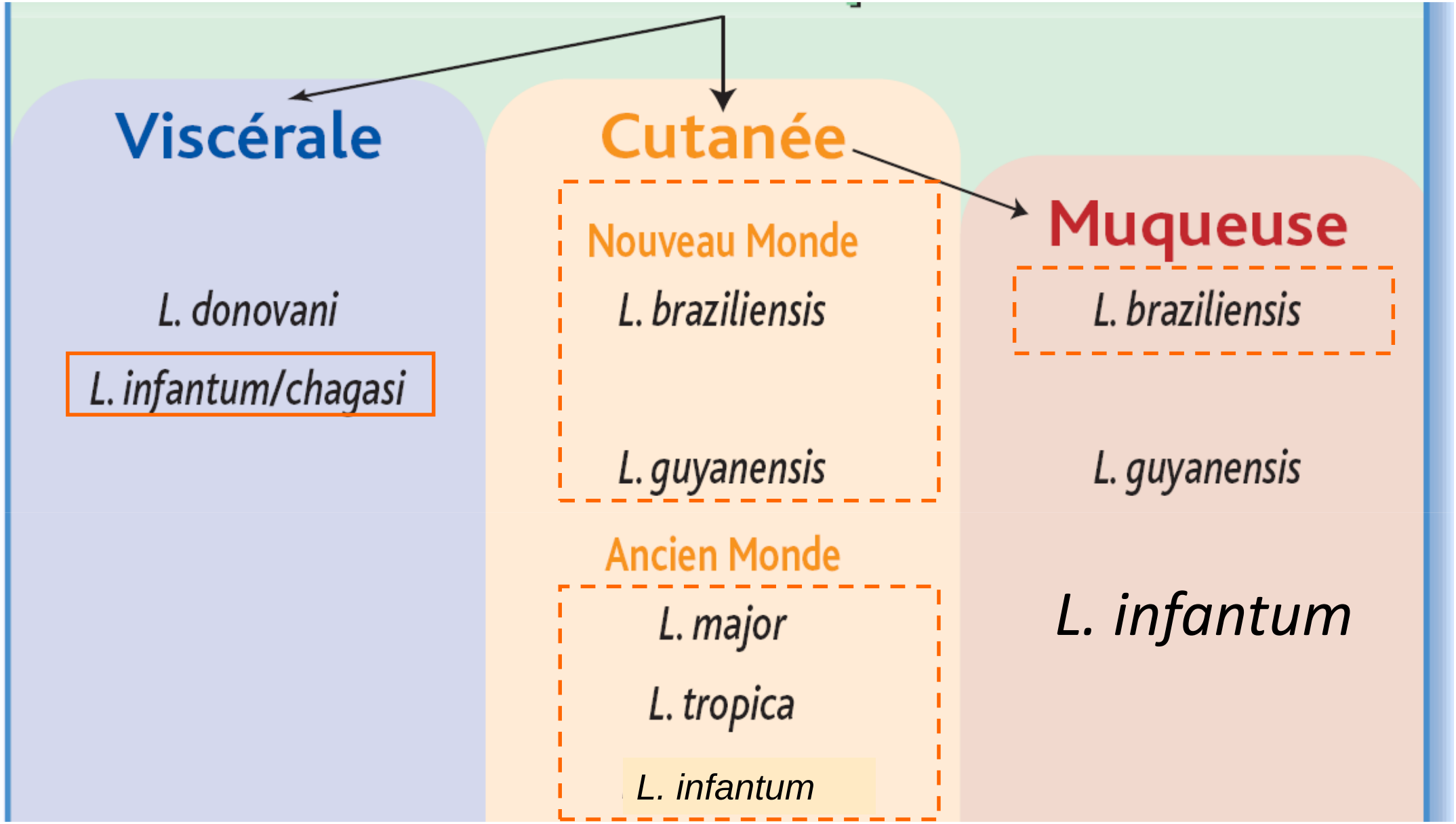


Cutanée



LEISHMANIA SPP	LEISHMANIA SUBGENUS	DISTRIBUTION: OLD WORLD	DISTRIBUTION: NEW WORLD	PRIMARY FORM	SECONDARY FORMS	ANTHROPONOTIC: AREAS OF TRANSMISSION	ZOONOTIC: RESERVOIR	ALTERNATIVE NAME
L. donovani	Leishmania	South East Asia (India, Bangladesh, Nepal, Sri Lanka) and East Africa		Visceral	Post–kala-azar dermal Cutaneous, mucosal, OIVL	South East Asia East Africa		Kala-azar
L. infantum (L. chagasi)	Leishmania	Europe Asia	South and Central America	Visceral	Cutaneous, mucosal Opportunistic*		Canid	
L. major	Leishmania	Asia, North & East Africa, Europe		Cutaneous			Rodent	Biskra nail
L. tropica	Leishmania	Asia, Europe		Cutaneous	Recidivans	Syria Afghanistan	Rodent	Aleppo boil
L. aethiopica	Leishmania	Ethiopia		Cutaneous	Diffuse cutaneous		Hyrax	
L. mexicana	Leishmania		Central America	Cutaneous			Rodent	Chiclero ulcer
L. amazonensis	Leishmania		Central and South America	Cutaneous	Diffuse cutaneous		Rodent	
L. braziliensis	Viannia		South America	Cutaneous, mucosal	Disseminated cutaneous Lymph		Rodent, marsupial	ML-espundia
L. panamensis	Viannia		Central and South America	Cutaneous	Mucosal Nodular lymphangitis		Edentate rodent	Ulcera de bejuco
L. guyanensis	Viannia		South America	Cutaneous	Mucosal Nodular lymphangitis		Rodent, edentates	Pian bois
L. peruviana	Viannia		South America	Cutaneous			Canid	Uta
L. martiniquensis/siamensis	Leishmania	South East Asia/West Indies		Cutaneous, visceral	Diffuse cutaneous			

From Buffet, Croft and Chatterjee. Cecil's Internal Medicine textbook 2023


Viscérale
L. donovani
L. infantum/chagasi
Cutanée
Nouveau Monde
L. braziliensis
L. guyanensis
Ancien Monde
L. major
L. tropica
L. infantum
Muqueuse
L. braziliensis
L. guyanensis
L. infantum

Epidémiologie

- Leishmaniose en France métropolitaine (CNR)
- Environ 100 cas par an

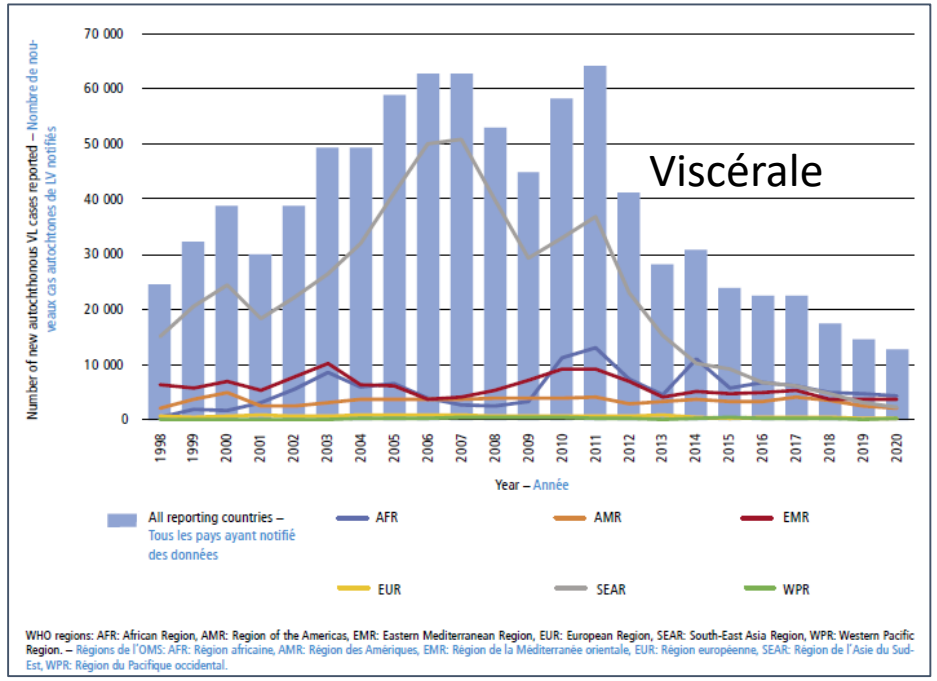
- <u>Leishmaniose viscérale = 1/3 des cas (30-40 /an)</u>
  - 80% autochtone (*L. infantum*) 20% Importée (*L. infantum L. donovani*)
  - Enfants100%immunocompétents Adultes 50% immunodéprimés (*VIH ou Iatrogène*) > 50% CD4 < 200/mm3

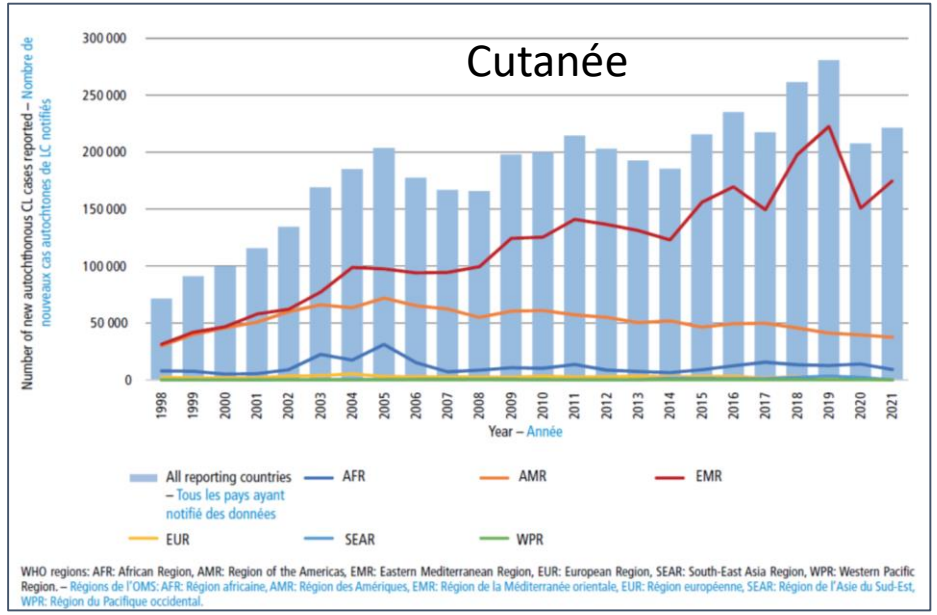
Antagonistes du TNFα

- <u>Leishmaniose cutanée = 2/3 des cas (60-70/an)</u>
  - Autochtone < 5% (*L. infantum*) (- Autochtone Guyane 100 – 350 cas/an)
  - Importée *L. major* > *L. braziliensis* > *L. infantum* > *L. tropica* >> Reste

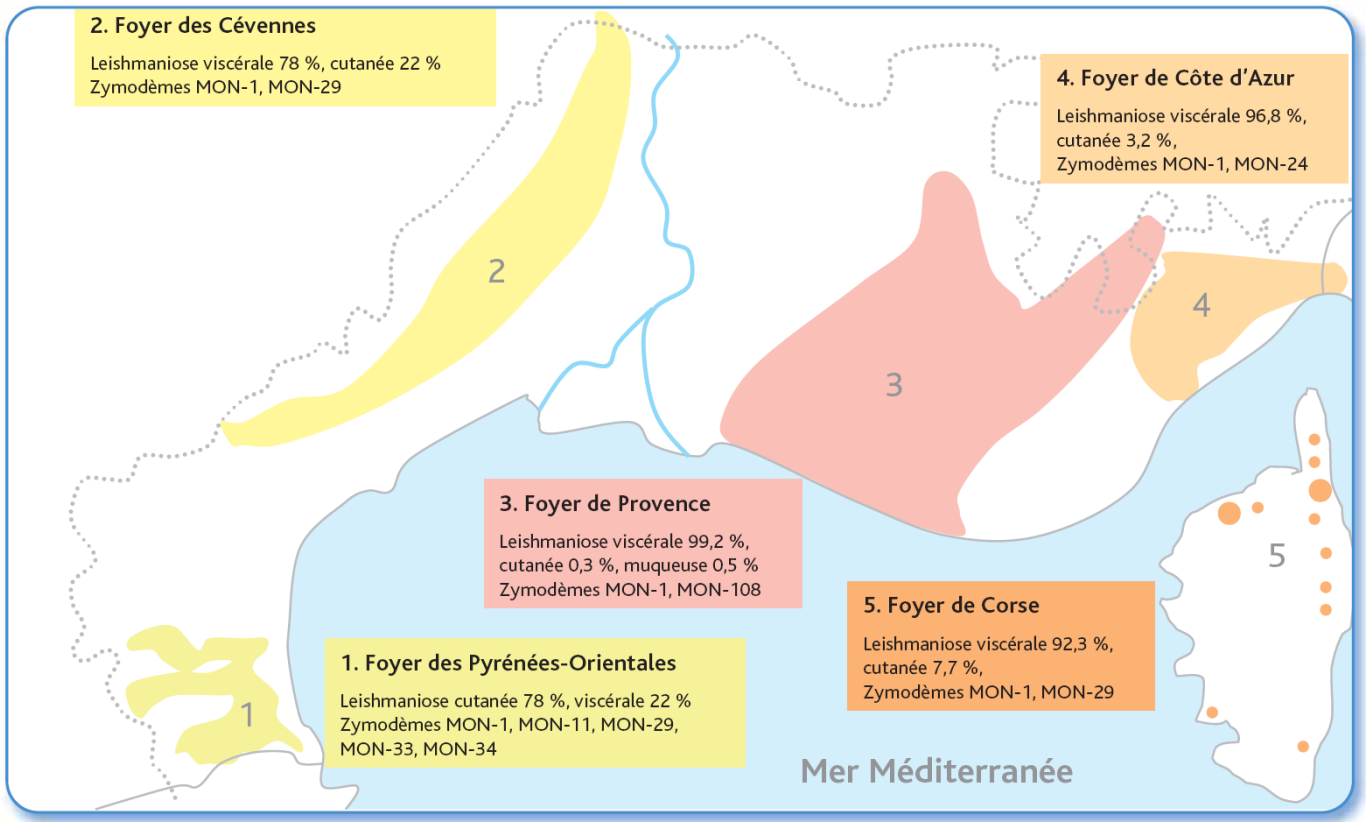
- Leishmaniose muqueuse 1 – 3 cas / an

Leishmaniose dans le monde

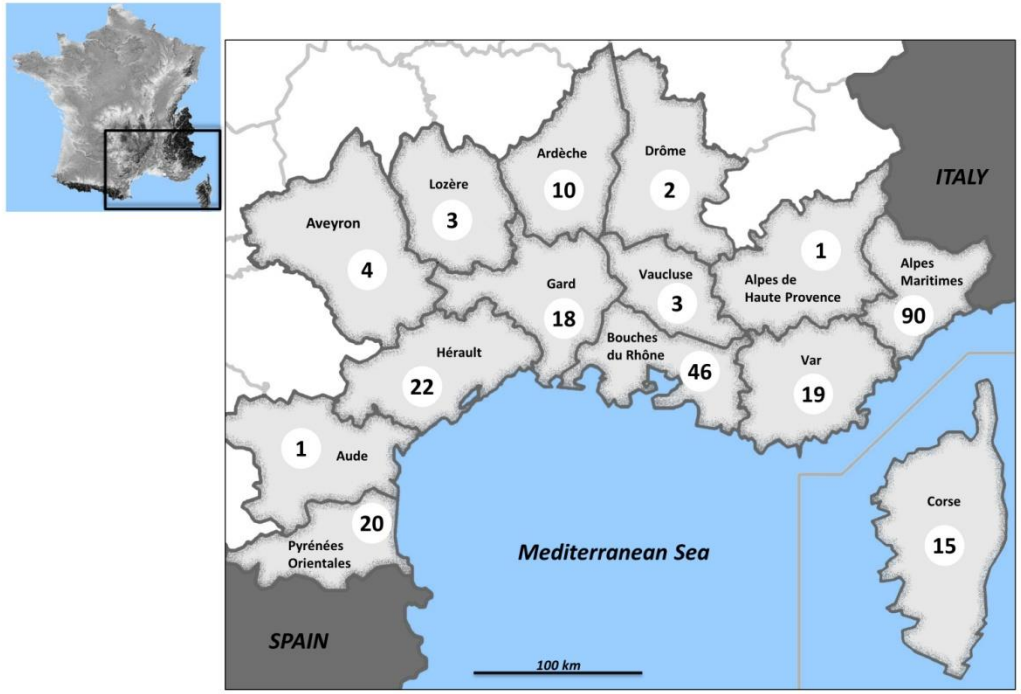




WHO, Weekly Epidemiological Record, 2021

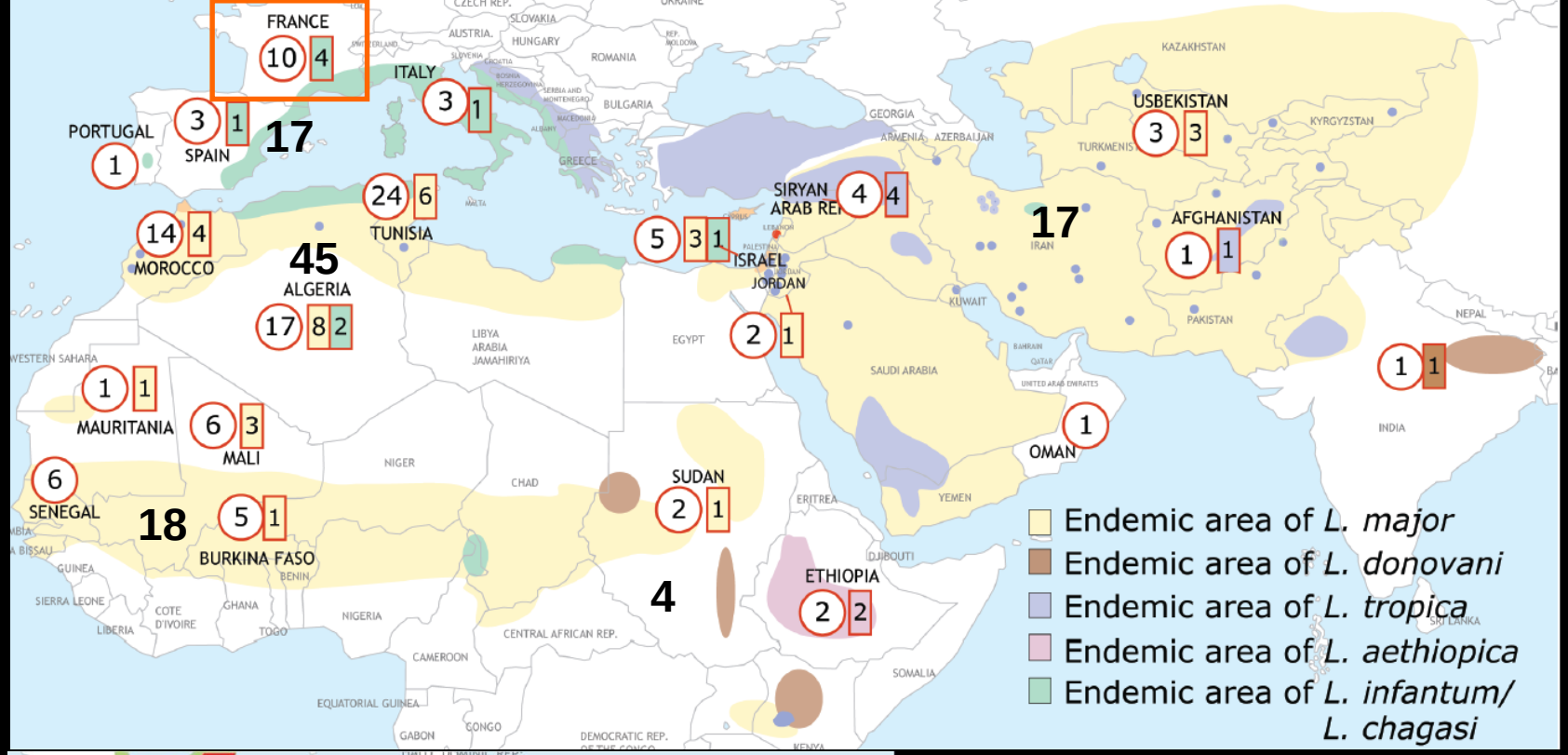


Pratlong et al.

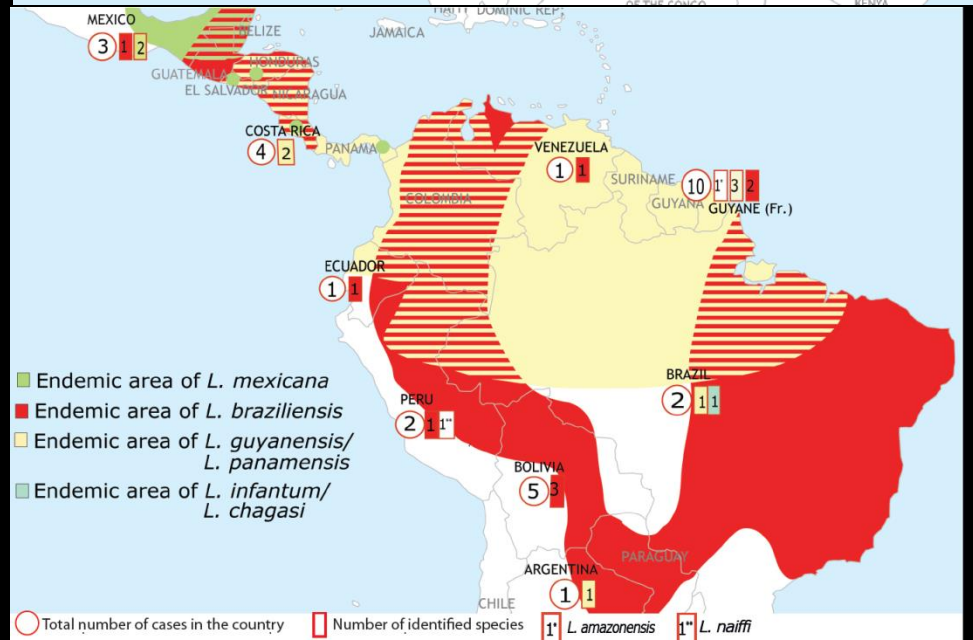


Lachaud et al.

111


FRANCE 10 4
ITALY 3 1
PORTUGAL 1
SPAIN 3 1
17
24 6
TUNISIA
14 4
MOROCCO
45
ALGERIA
17 8 2
5 3 1
SIRYAN ARAB REP. 4 4
ISRAEL
JORDAN
2 1
17
USBEKISTAN 3 3
AFGHANISTAN 1 1
1 1
1 1
OMAN
1 1
MAURITANIA
6 3
MALI
6
SENEGAL
18
5 1
BURKINA FASO
SUDAN 2 1
4
ETHIOPIA 2 2
Endemic area of L. major
Endemic area of L. donovani
Endemic area of L. tropica
Endemic area of L. aethiopica
Endemic area of L. infantum/ L. chagasi

29


MEXICO 3 1 2
COSTA RICA 4 2
VENEZUELA 1 1
SURINAME
GUYANA
10 1' 3 2
GUYANE (Fr.)
ECUADOR 1 1
PERU 2 1 1"
BRAZIL 2 1 1
BOLIVIA 5 3
ARGENTINA 1 1
Endemic area of L. mexicana
Endemic area of L. braziliensis
Endemic area of L. guyanensis/ L. panamensis
Endemic area of L. infantum/ L. chagasi
Total number of cases in the country
Number of identified species
1' L. amazonensis
1" L. naiffi

Guéry et al. 2021 PLoS NTD

Base de données du Consortium LeishMan

756 Patients/Episodes/Echantillons
entre le 04/01/2006 et le 05/30/2019

705 **Patients/Episodes/Echantillons**
Cutanés ou viscéraux
Avec date de déclaration

65 épisodes de
Leishmaniose Viscérale (24 patients)
162 doublons*

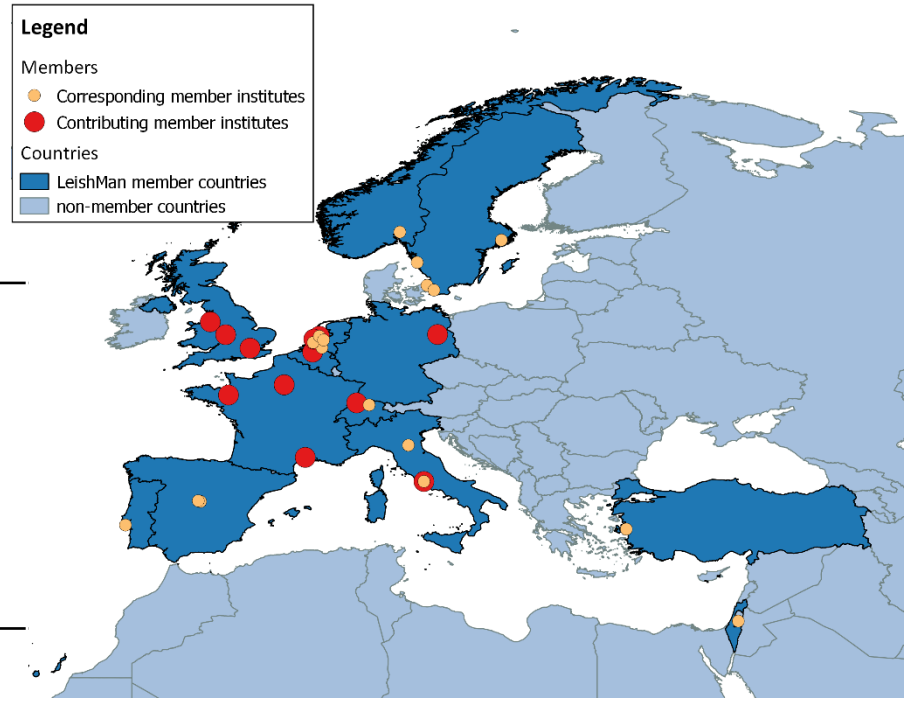
478 épisodes d'atteinte tégumentaire

14 épisodes sans description clinique

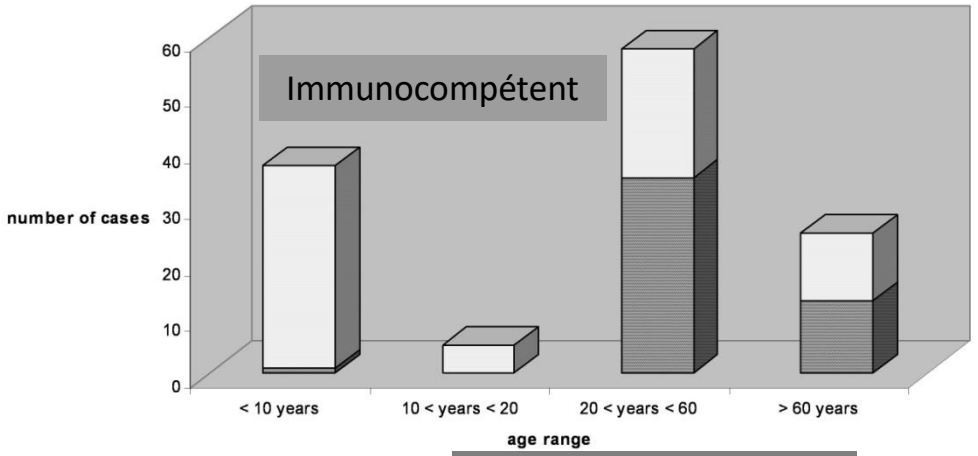
464 épisodes
de leishmaniose tégumentaire
chez 459 patients

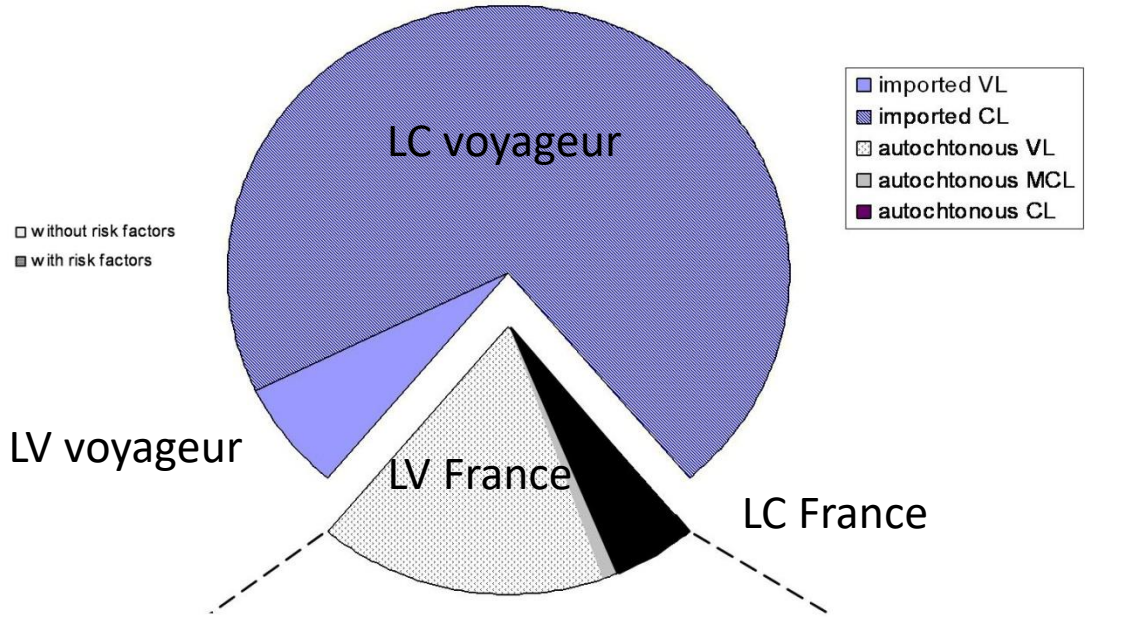
Identification de l'espèce infectante
198 patients

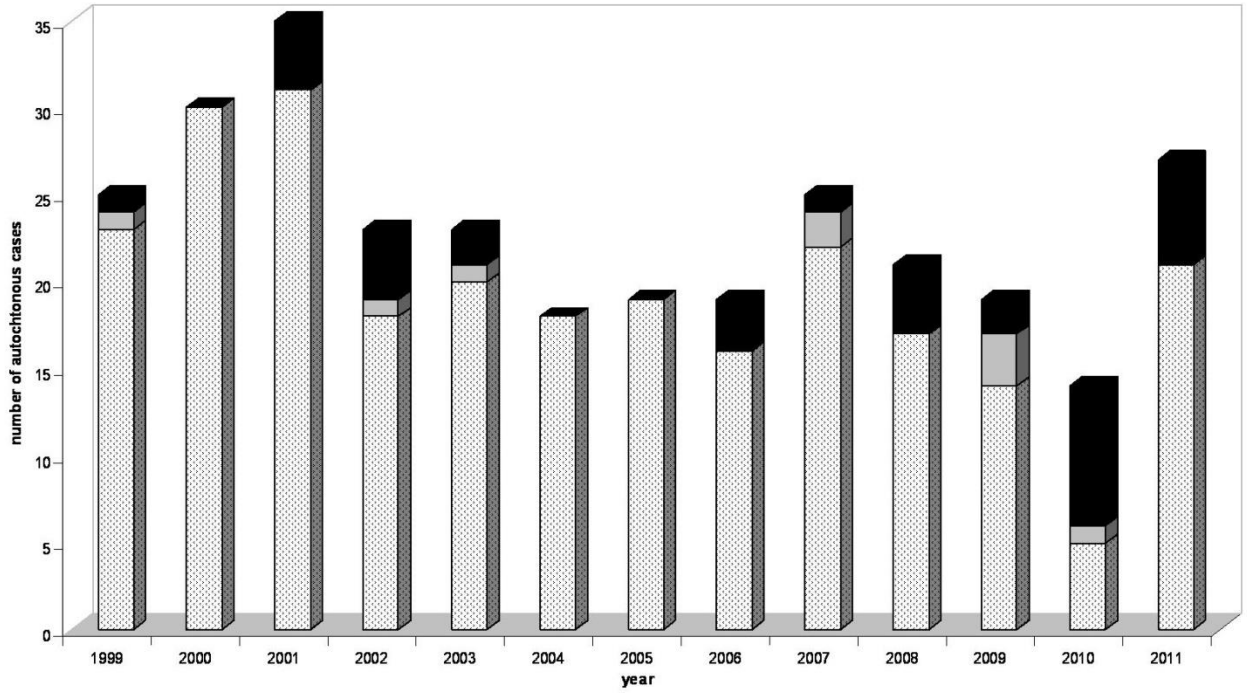
Countries	Cases, n(%)
France	217 (47)
U.K	85 (18)
Germany	60 (13)
Switzerland	45 (10)
Netherlands	38 (8)
Belgium	12 (2,5)
Sweden	7 (1,5)
Total	**464**



Centres	Cases, n(%)
AMC Amsterdam	38 (8)
BHH Birmingham	1 (0,5)
CHU Rennes	31 (7)
CNR Montpellier	1 (0,5)
HTD London	84 (18)
ITM Antwerpen	12 (2)
ITMIH Berlin	60 (13)
Necker-Pasteur-Pitié Paris	185 (40)
Public Health Agency of Sweden	7 (1)
STPHI Basel	45 (10)
Total	**464**







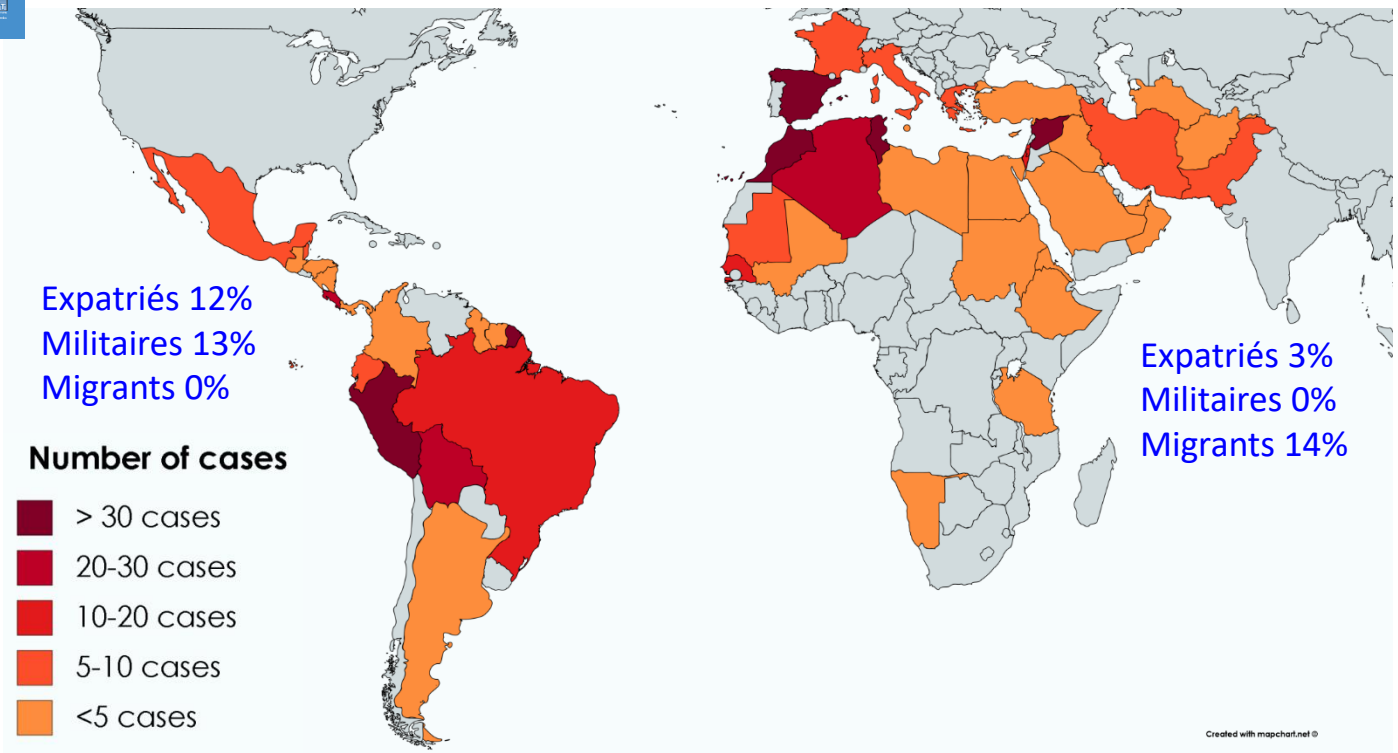
Lachaud et al. Eurosurveillance 2013

Guéry et al. 2021 PLoS NTD

Qui sont les patient.e.s ?
D'où reviennent-elles . ils ?

Guyane française	41
Perou	37
Costa Rica	28
Bolivie	21

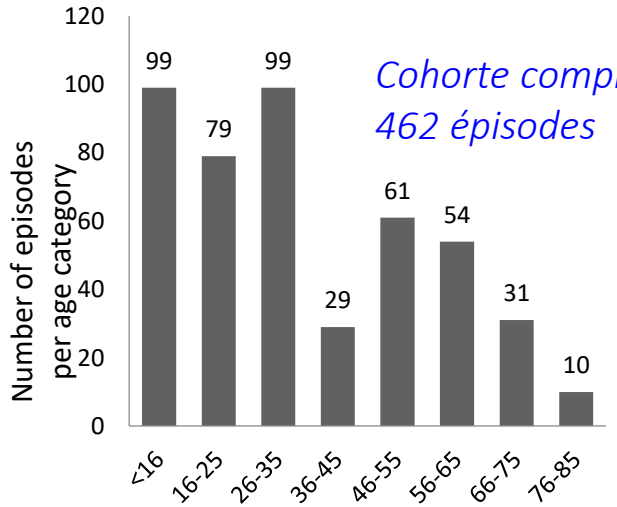
Enfants :
21 %



France 9

Espagne	48
Syrie	36
Maroc	34
Tunisie	32

Jeunes de plus de 65 ans :
9 %



Cohorte complète
462 épisodes

18

Diagnostic clinique et biologique

Asymptomatique

Infection

Asymptomatique ou cicatrice

Viscérale

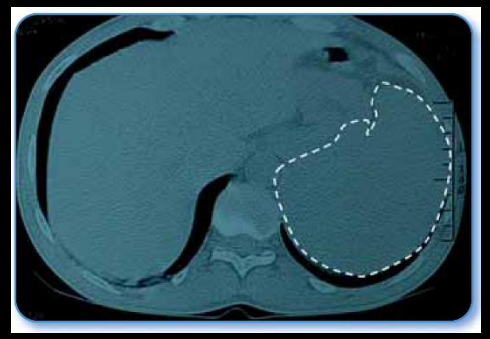
Cutanée

Muqueuse

PKDL

Leishmaniose cutanée Post-KalaAzar

Macules papules diffuses après une leishmaniose viscérale



Fièvre (FPI)

Splenomegalie

Hepatomegalie

Adénopathies

Cytopénies

Immunodépression (2 – 50%)

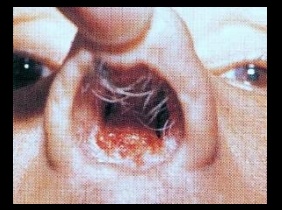
Ulcères & Nodules froids Lymphangite

Limites nettes

Subaigu / chronique

Pas de signes généraux

Immunodépression « rare »



Infiltration muqueuse nasale

Croûtes Ulcérations

Subaigues Chroniques

Immunodépression rare

Diagnostic
Leishmaniose viscérale

Chez l'immunocompétent la sérologie a une excellente valeur prédictive négative car a une sensibilité élevée (à l'exception des 2 premières semaines de fièvre)

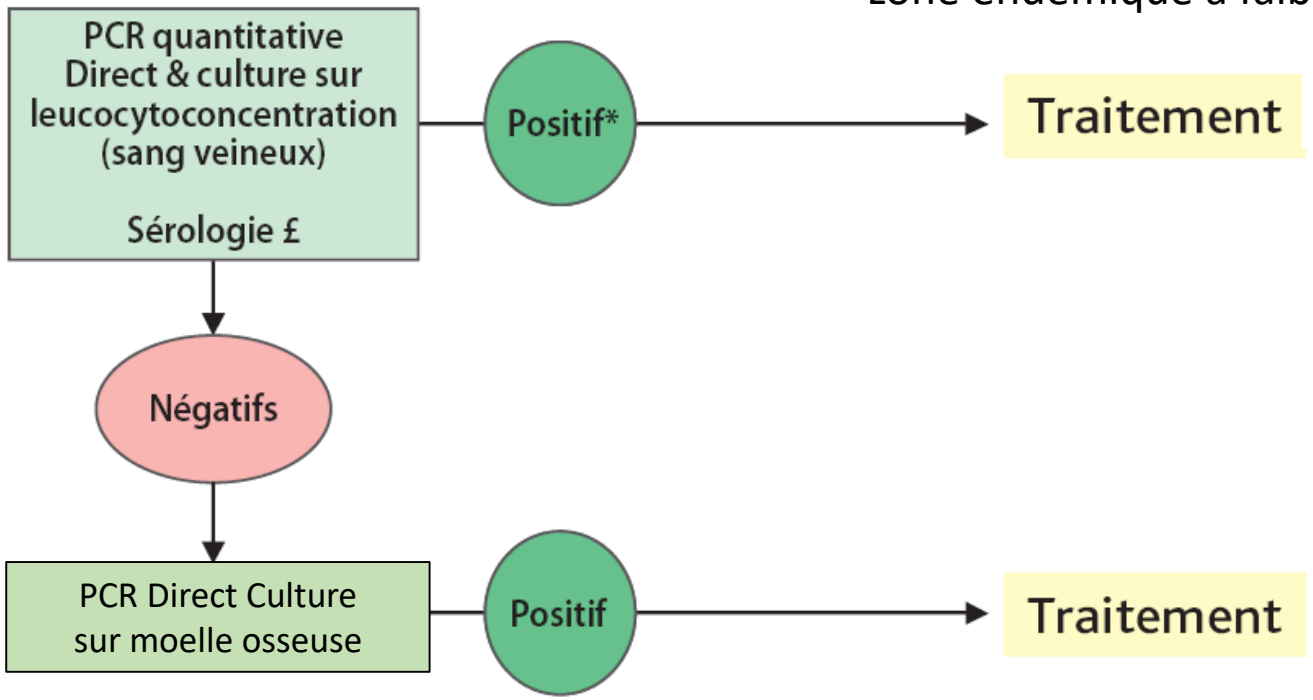
Limite de spécificité chez le résident en zone endémique (psoitivité chez les sujets asymptomatiques)

Tests bandelette sérologiques utilisés en zone endémique à faible ressource

PCR curieusement
un peu plus sensible
sur plasma que sur sang total

Algorithme diagnostique : leishmaniose viscérale

Suspicion clinique
Splénomégalie fébrile (+/- hépatomégalie)
Fièvre prolongée inexpliquée AEG
Cytopénie
Séjour (même très ancien) en zone endémique



Am. J. Trop. Med. Hyg., 75(5), 2006, pp. 858–863

REFERENCE VALUES FOR *LEISHMANIA INFANTUM* PARASITEMIA IN DIFFERENT CLINICAL PRESENTATIONS: QUANTITATIVE POLYMERASE CHAIN REACTION FOR THERAPEUTIC MONITORING AND PATIENT FOLLOW-UP

CHARLES MARY,* FRANÇOISE FARAUT, MARIE-PIERRE DROGOUL, BERNARD XERIDAT, NICOLAS SCHLEINITZ, BERNADETTE CUISENIER, AND HENRI DUMON

Laboratoire de Parasitologie, Hopital de la Timone, Marseille, France; Centre d'Information et de Soins de l'Immunodéficience Humaine, Hopital Sainte Mrguerite, Marseille, France; Polyclinique Clairval, Marseille, France; Medecine Interne, Hopital de la Conception, Marseille, France; Laboratoire de Parasitologie, Hopital du Bocage, Dijon, France

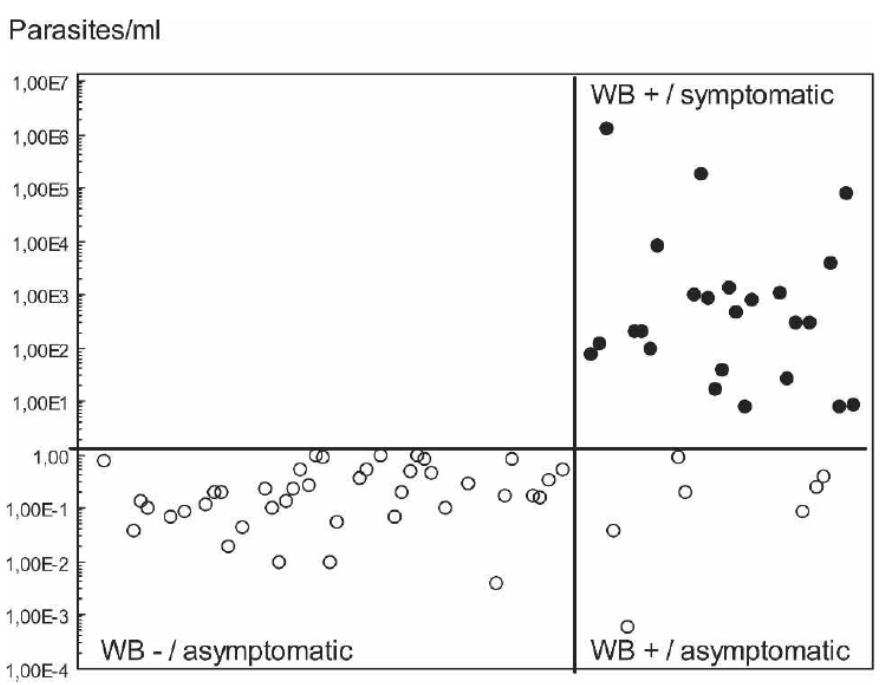
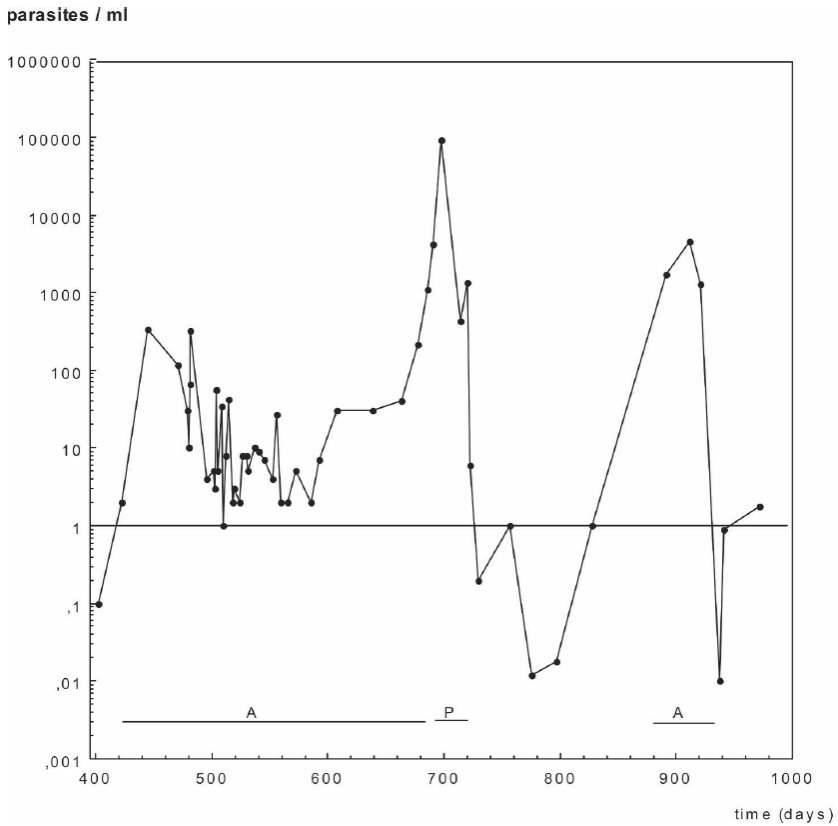


FIGURE 1. Distribution of parasitemias of asymptomatic subjects (○) and visceral leishmaniasis patients at diagnosis (●). WB = Western blot.



Diagnostic
Leishmaniose cutanée

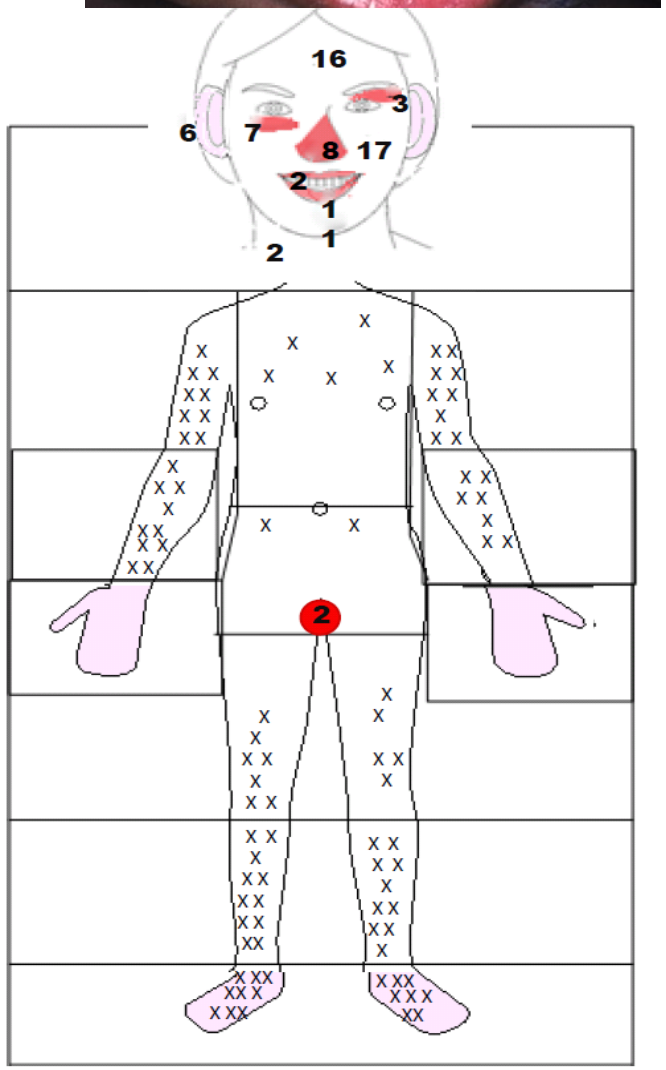


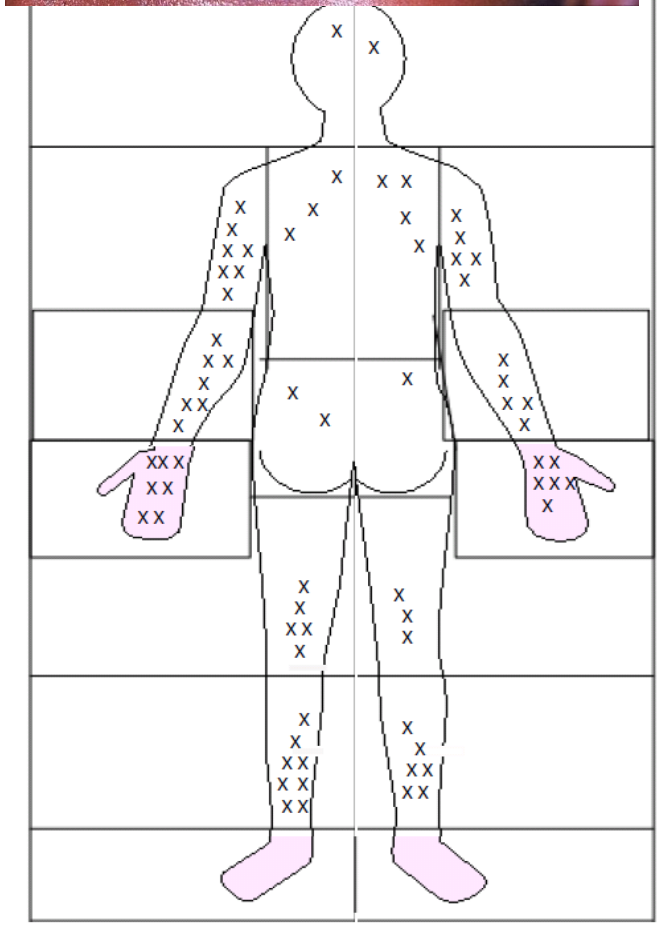










N (%) of total body lesions

Nose, lips, eyelids: 21 (9)

Ears: 6 (3)

Other headlesions: 39 (17)
(cheeks, chin, forehead)

Arms &
forearms: 59 (25)

Trunk: 17 (7)

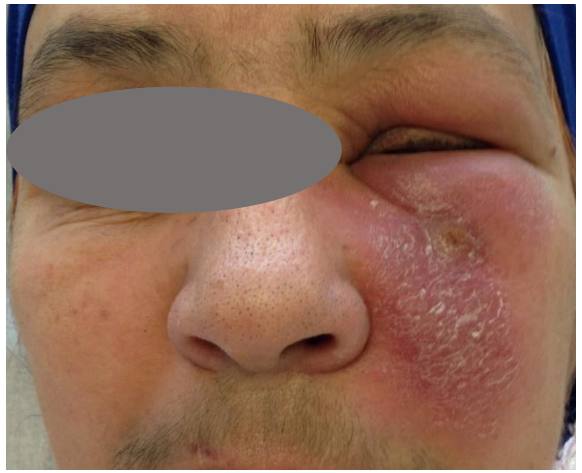
Genitalia: 2 (1)

Hands: 16 (7)

Thighs, &
legs: 55 (24)

Feet: 17 (7)

Total lesions: 232 (100)









Dr Lama Jalouk

Dr Lama Jalouk


Leishmaniose cutanée
Lente Infiltrée
Limites nettes
Arrondie ou ovale

	N or median	% or IQ 25-75
Duration of symptoms (months)	3	2-6
Number of lesions	2	1-3
Main lesion-Ulceration diameter (mm)	15	4-30
Main lesion-Induration diameter (mm)	20	13-34
Main lesion-type		
Ulcer	*91*	*60*
Papulonodular	*28*	*19*
Dry crust	*17*	*11*
Squamous plaque	*9*	*6*
Other	*5*	*3*
Lymphatic involvement	19	11
Mucosal involvement	1	1
Secondary infection	14	9
Satellite lesions	2	1-3

Incubation:
3 semaines - 3 mois

Délai diagnostic: 3 mois

Nombre de lésions: 1-3

Ulcération: 60%

Atteinte lymphatique 10%
Surinfection 5-10%

Atteinte muqueuse 1%

Guéry et al. 2021 PLoS NTD

Quelles sont les principales formes cliniques ? Diffèrent-elles au retour de l'Ancien et du Nouveau Monde ?

Les formes muqueuses ne sont pas plus fréquentes au retour du Nouveau Monde que de l'Ancien Monde

	New World	Old World	p-value
	185 episodes	279 episodes	
Age, median [IQR]	30 [24-38]	32 [10-58]	0,81
Male	74.6% (138)	54.5% (152)	**<0,01**
Immunocompromised	0.6% (1/177)	8% (21/264)	**<0,01**
Type of tegumentary leishmaniasis			
Localized Cutaneous	96% (178)	94% (262)	
Muco-cutaneous	1.62% (3)	2.51% (7)	
Mucosal	1.08% (2)	2.51% (7)	
PKDL	0.54% (1)	0.36% (1)	
Disseminated cutaneous leishmaniasis	0.54% (1)	0.36% (1)	
Muco-cutaneous and visceral leishmaniasis	0% (0)	0.36% (1)	

PKDL Leishmaniose Cutanée Post-Kala-Azar

Les formes rares sont rares Mais l'immunodépression n'est plus exceptionnelle

Guéry et al. 2021 PLoS NTD

Peut-on apprécier plus précisément les corrélations entre espèce infectante et présentation clinique ?

Evolution plus rapide, moins multi-lésionnelle, avec plus de dissémination lymphatique dans le nouveau monde que dans l'ancien monde

	New World	Old World	p-value
	185 episodes	279 episodes	
Delay from first symptoms to parasitological diagnosis (months), median [IQR]	2 [1-3]	4 [2-6]	<0,01
Duration of disease (in months), median [IQR]	3 [2-4]	4 [3-7]	<0,01
Number of lesions	1 [1-2,25]	2 [1-4]	<0,01
Diameter of largest lesion (millimeter), median [IQR]	30 [20-43.5]	20 [10-35)	<0,01
Nodular lymphangitis	30.27% (56)	5.73% (16)	<0,01

	L. braziliensis complex n = 34	*L. guyanensis* complex n = 18	*L. major* complex n = 52	*L. tropica* complex n = 26	*L. donovani* complex n = 36
Diameter of largest lesion (mm), median [IQR]	30 [20–39]	40 [25–50]	30 [15–43]	20 [10–30]	7 [3–12]
Nodular lymphangitis	35% (12)	44% (9)	12% (6)	12% (3)	1 [1–2]
Mucosal involvement	6% (2) ML (1) MCL(1)	5% (1) MCL (1)	0% (0)	0% (0)	22% (8) ML(4) MCL(4)

Note. Data are % (n) unless indicated. Abbreviations: IQR, interquartile range

Infecting species	*L. braziliensis/L. guyanensis* N=52	*L. major* N=52	*L. tropica* N=26	*L. infantum* N=36
Type and location of skin lesions Lesion(s) 0-9% of lesions 10-19% of lesions 20-29% of lesions 30-39% of lesions 40-50% of lesions	 **Ulcer 85%** *Lymphangitis 40%* **1 lesion** [1-3] ; **30 mm** [20-50]	 **Ulcer 63%** **Papule or nodule** 23% *Lymphangitis 12%* **4 lesions** [2-8] ; **30 mm** [15-43]	 **Ulcer 35%** **Papule** 31% **Squamous or Crust** 30% *Lymphangitis 12%* **1 lesion** [1-2] ; **20 mm** [10-30]	 **Ulcer 47%** **Squamous or Crust** 28% **Papule** 25% *Lymphangitis 6%* **1 lesion** [1-2] ; **20 mm** [10-23]
Skin lesions: **-number, median** [IQR] **-size, median** [IQR]				
Demographics **Median age** [IQR]	**Young male** (71%) **28 year-old** [24-35]	**Children & young adults** **18 year-old** [6-45]	**Children & adults** **26 year-old** [11-75]	**Middle-age adult** **56 year-old** [47-66]
Immunocompromised	0%	6%	0%	18%

Leish or not Leish? That is the question

Leishmaniasis

Sporotrichosis

Pyodermitis

Staphylococcus aureus

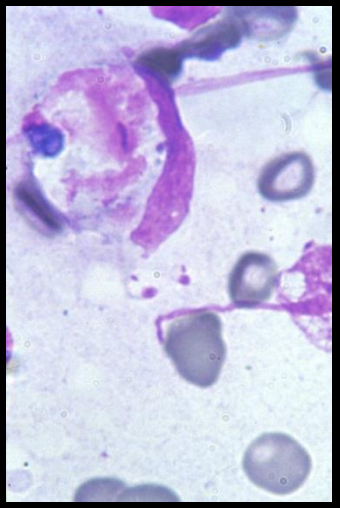
Sporotrichosis

Pyodermitis

Group A Streptococcus

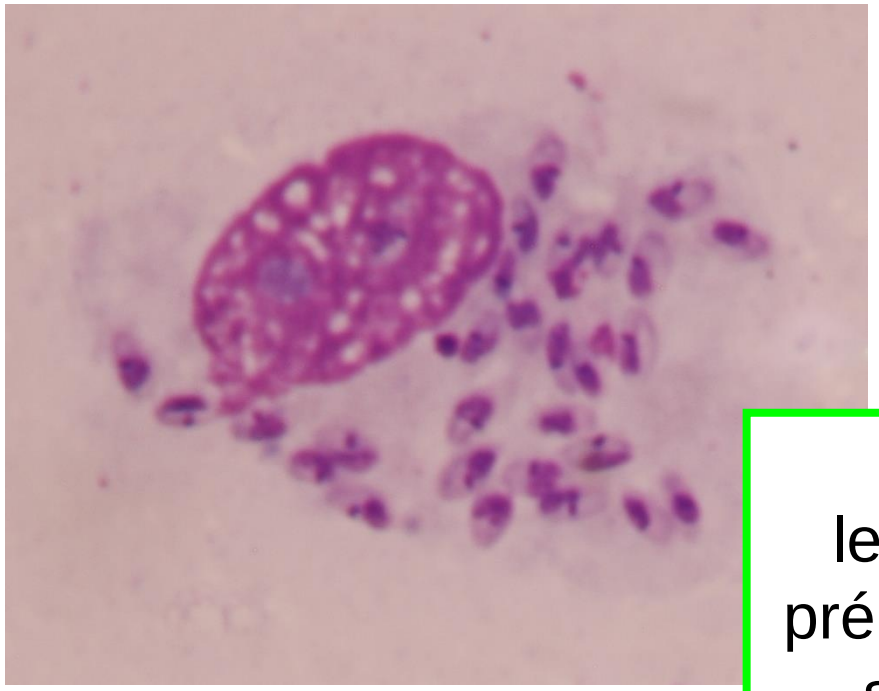
Leishmaniasis

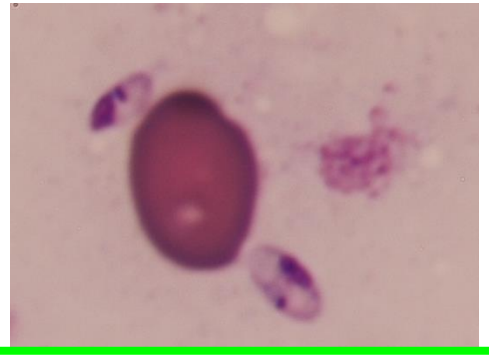
Diagnostic parasitologique

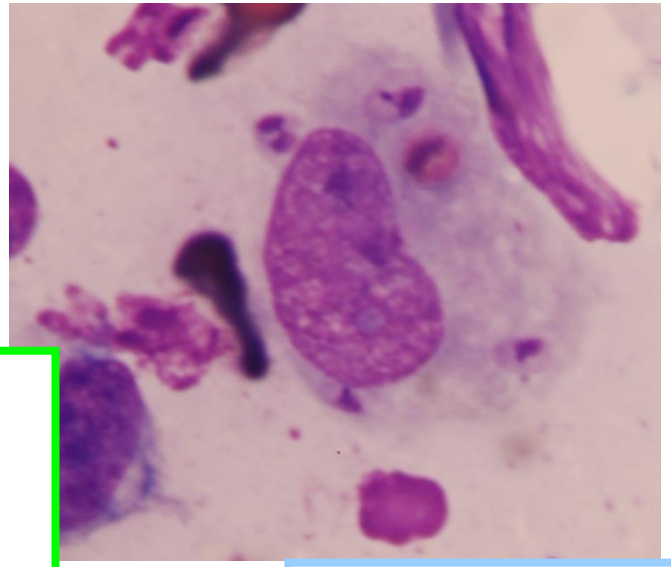


Bandelette (?)

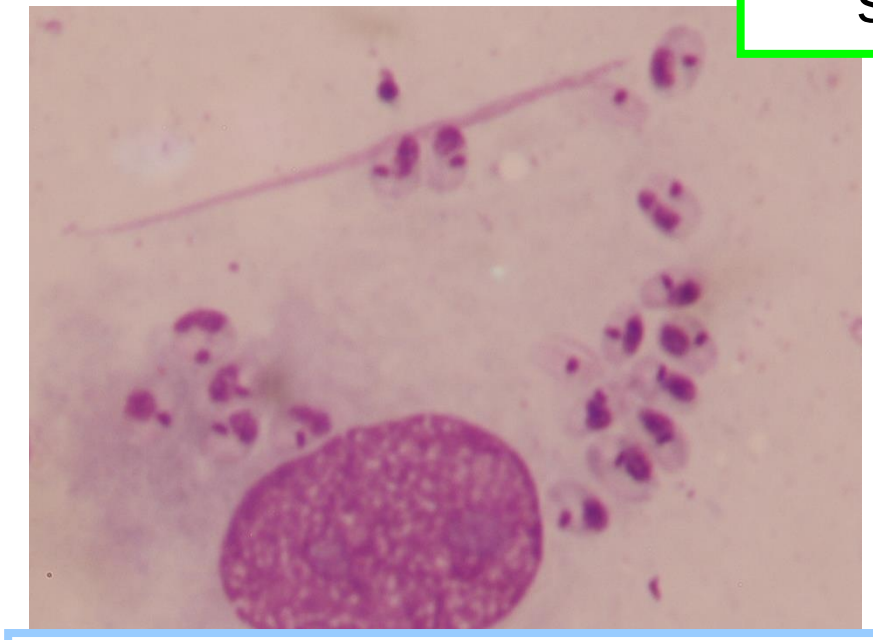
>Direct PCR

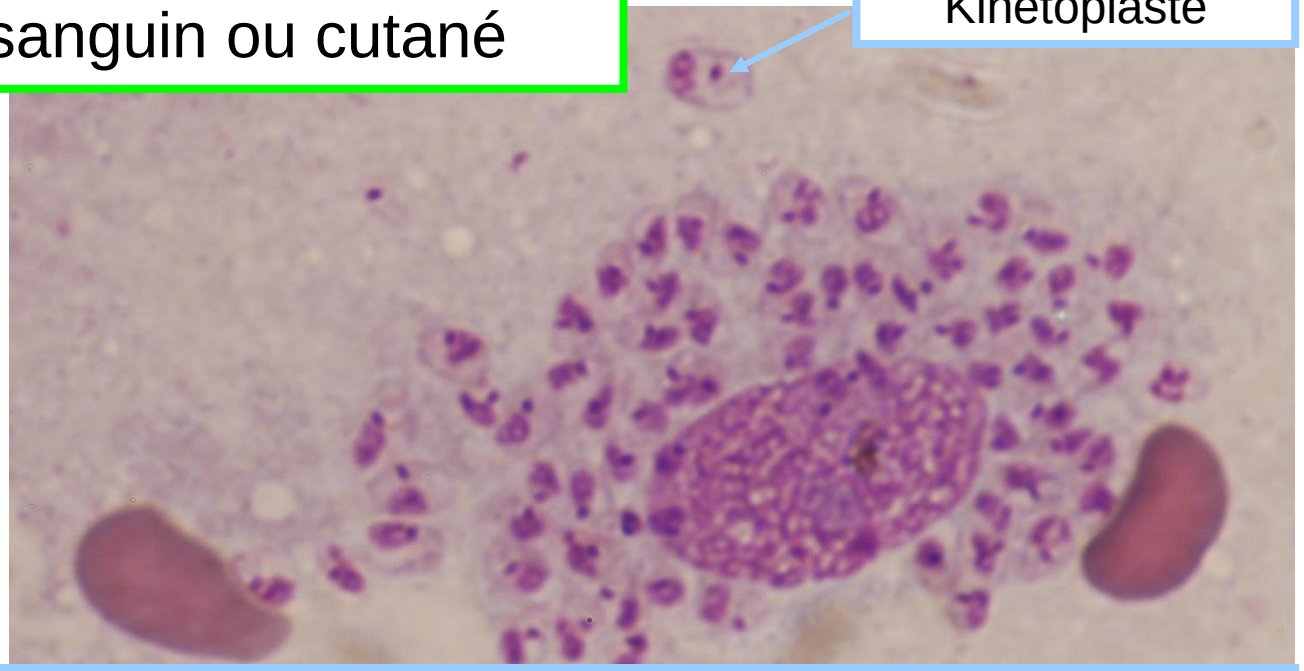






Amastigotes de leishmanies dans un prélèvement médullaire, sanguin ou cutané

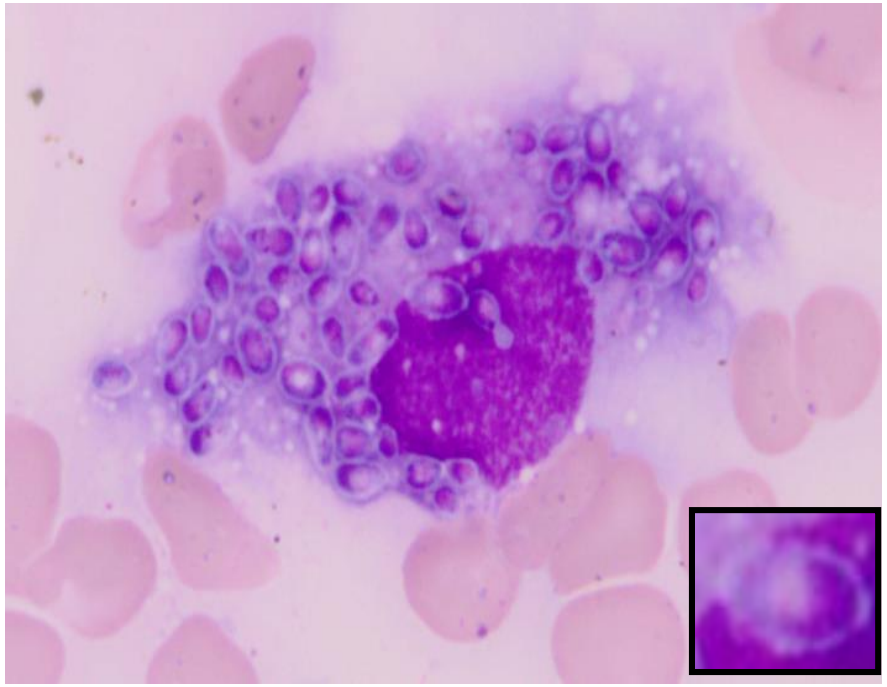




Kinétoplaste

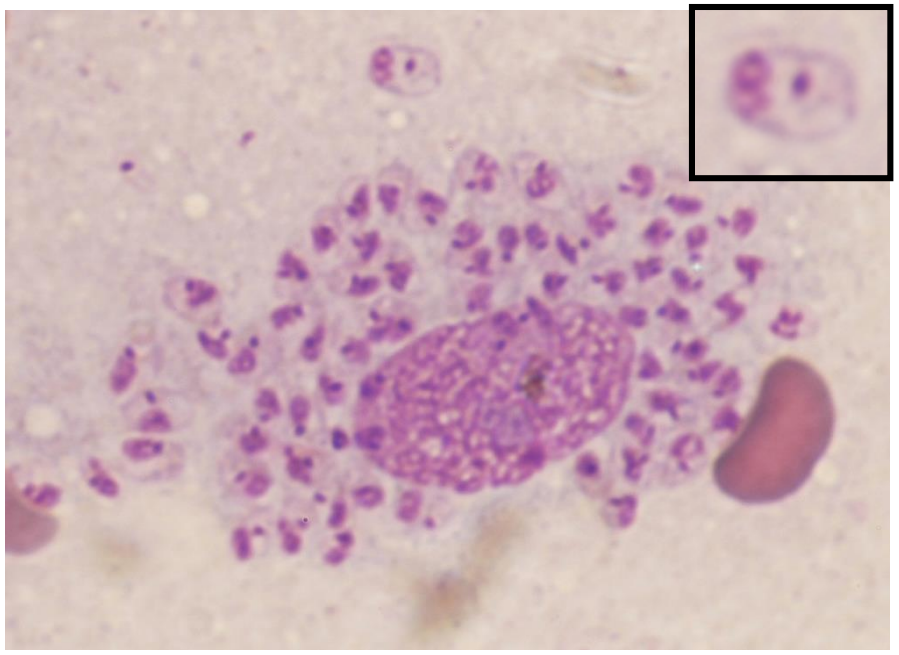
Pas de coloration réellement spécifiques (Giemsa)

Histo

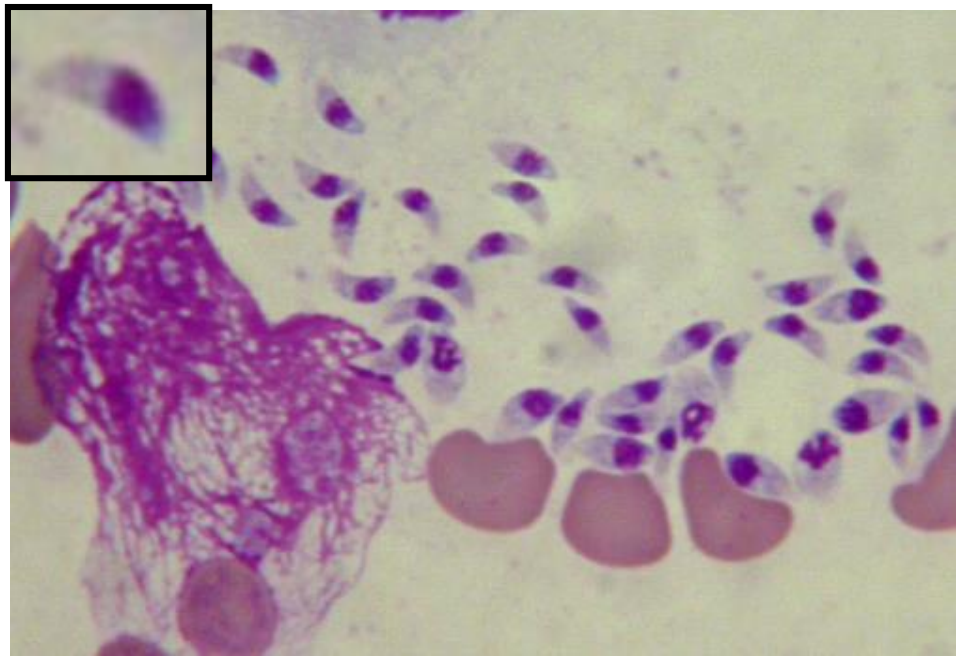


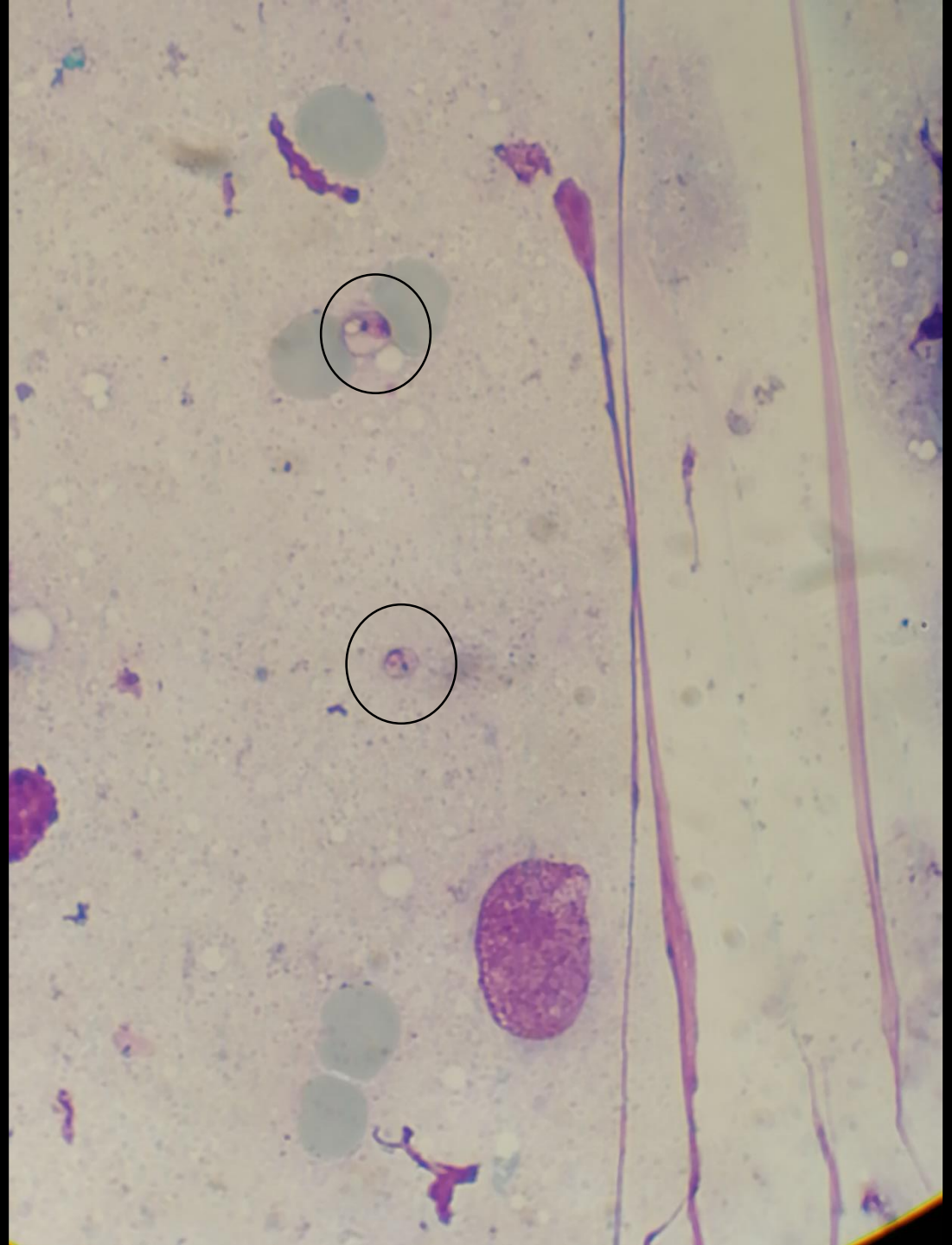
Histo

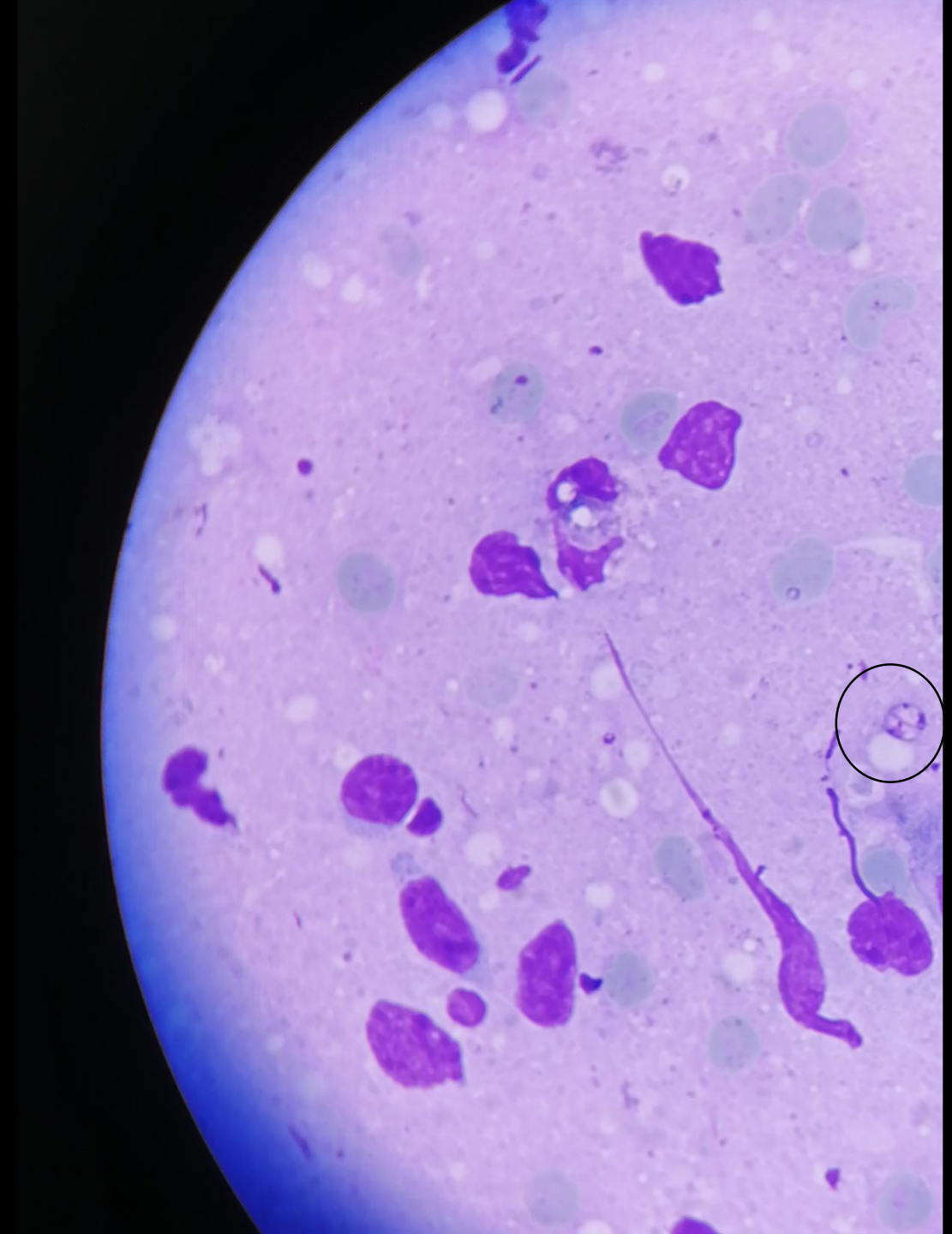
Leish

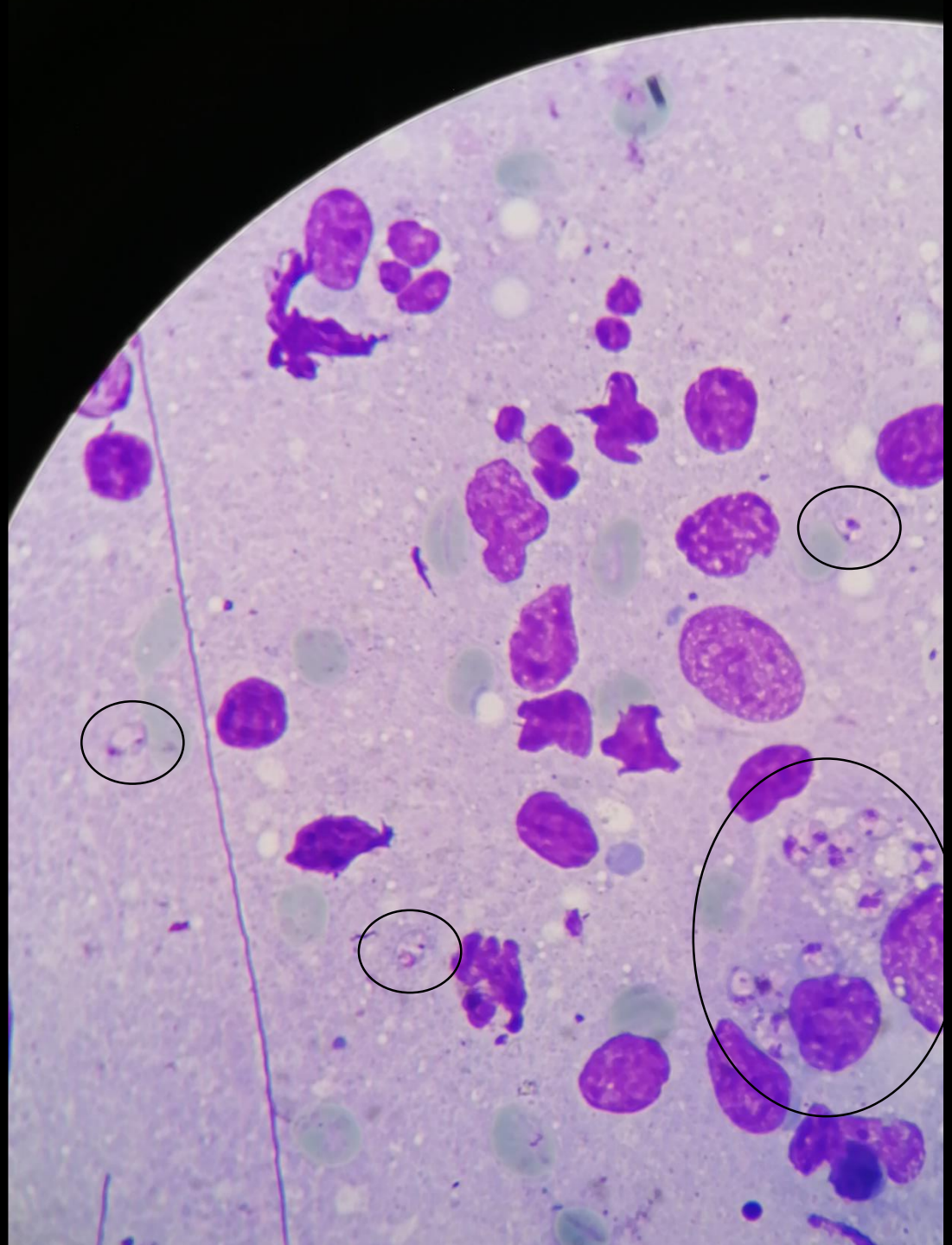


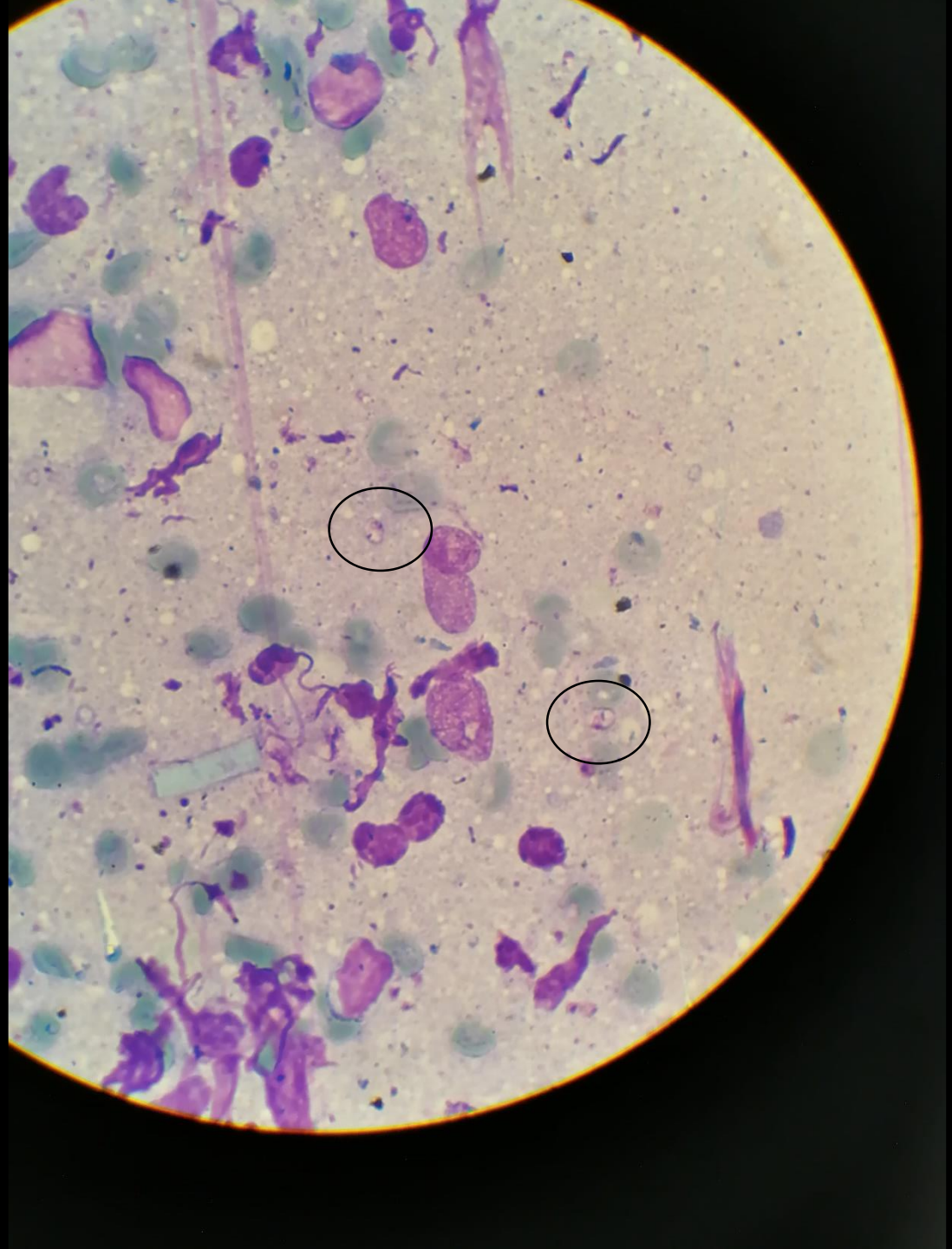
Toxo











Traitement

Traitement
Leishmaniose viscérale

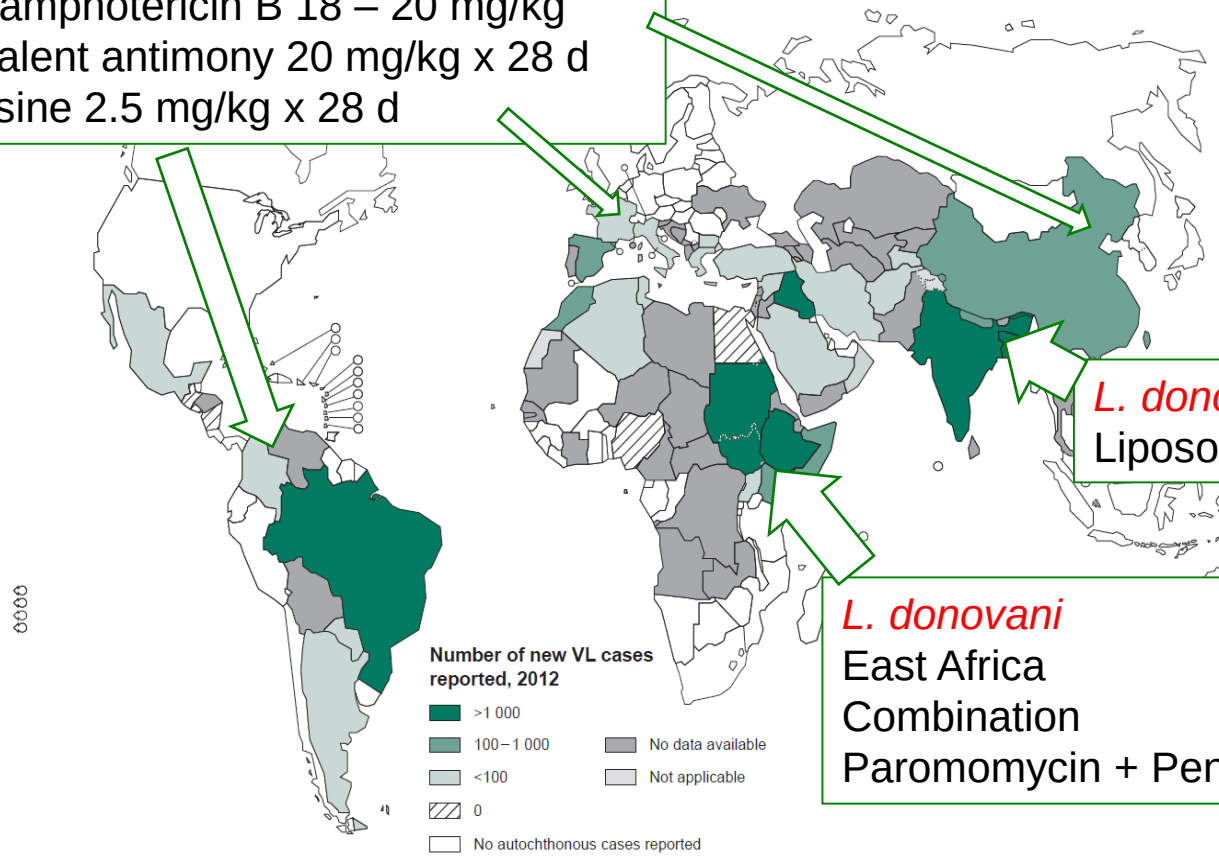
Fig. 4.9.1 Distribution of visceral leishmaniasis, worldwide, 2012

L. infantum
Liposomal amphotericin B 18 – 20 mg/kg
OR pentavalent antimony 20 mg/kg x 28 d
OR miltefosine 2.5 mg/kg x 28 d

L. donovani = priority
Public health Impact
Human reservoir

L. donovani Indian subcontinent
Liposomal amphotericin B single-dose

L. donovani
East Africa
Combination
Paromomycin + Pentavalent antimony

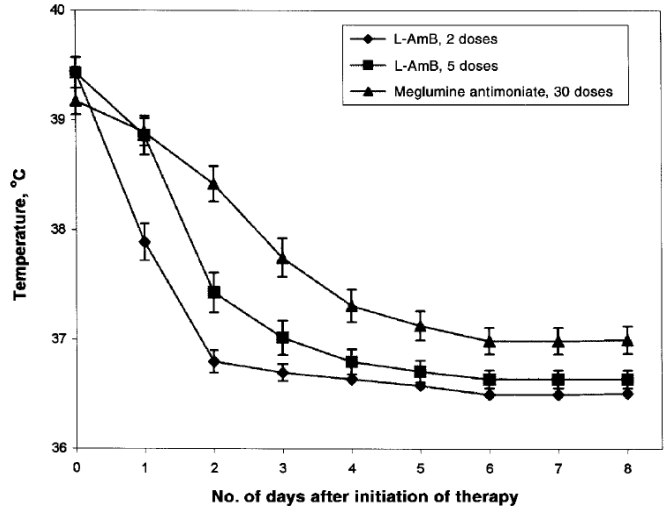


Two Doses of a Lipid Formulation of Amphotericin B for the Treatment of Mediterranean Visceral Leishmaniasis

Vassiliki Syriopoulou,[1] George L. Daikos,[2] Maria Theodoridou,[1] Ioanna Pavlopoulou,[1] Archondia G. Manolaki,[1] Evagelia Sereti,[3] Aikaterini Karamboula,[1] Dimitra Papathanasiou,[1] Xenophon Krikos,[1] and George Saroglou[4]

[1]First Department of Pediatrics, Aghia Sophia Children's Hospital, [2]First Department of Propedeutic Medicine, Laiko General Hospital, and [3]Pentelis Children's Hospital and [4]School of Nursing, Athens University, Athens, Greece

Clinical Infectious Diseases 2003; 36:560–6



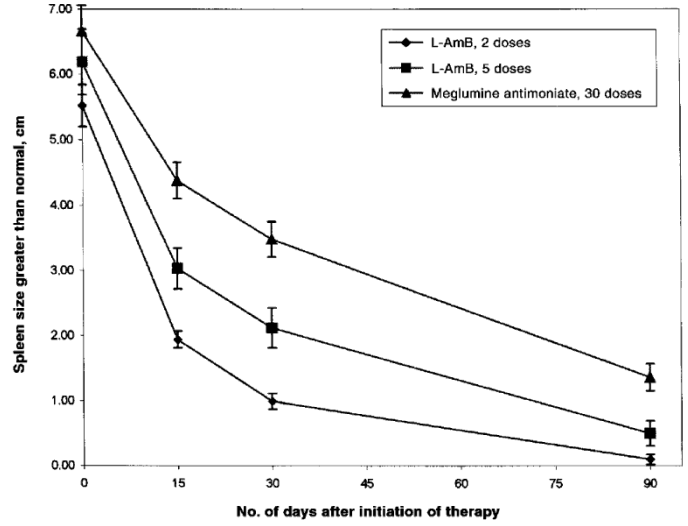


Table 2. Laboratory findings for 123 patients after initiation of therapy for visceral leishmaniasis (VL), according to treatment group.

Laboratory finding, no. of days after treatment initiation	L-AmB 2 Group A_1[a] (n = 41)	L-AmB 5 Group A_2[b] (n = 30)	Sb 20 x 30 Group B[c] (n = 52)	*P* value Group A_1 vs. group A_2	*P* value Group A vs. group B
Hemoglobin level, g/dL					
0	8.19 ± 0.16	7.39 ± 0.25	7.95 ± 0.17	.01	.30
15	11.12 ± 0.12	10.20 ± 0.17	9.57 ± 0.17	<.01	<.01
30	12.01 ± 0.14	11.30 ± 0.17	10.89 ± 0.14	<.01	<.01
90	12.50 ± 0.15	12.08 ± 0.17	11.70 ± 0.15	.06	<.01
WBC count, $\times 10^6$ cells/L					
0	4.81 ± 0.35	4.67 ± 0.42	4.04 ± 0.26	.79	.08
15	8.63 ± 0.16	8.57 ± 0.50	6.28 ± 0.28	.90	<.01
30	8.58 ± 0.30	8.80 ± 0.60	7.72 ± 0.17	.70	<.01
90	8.60 ± 0.22	8.34 ± 0.22	8.38 ± 0.40	.40	.60
Platelet count, $\times 10^9$ platelets/L					
0	112 ± 5.90	114 ± 6.70	113 ± 6.40	.83	.96
15	313 ± 7.20	290 ± 16.40	278 ± 17.00	.22	.07
30	424 ± 83.00	315 ± 15.20	312 ± 13.00	.20	.19
90	326 ± 12.00	326 ± 12.70	318 ± 10.50	.97	.65
Ratio of albumin to globulin, g/dL					
0	0.89 ± 0.03	0.80 ± 0.05	0.82 ± 0.03	.15	0.14
15	1.5 ± 0.03	1.27 ± 0.06	1.08 ± 0.05	<.01	<.01
30	1.70 ± 0.03	1.50 ± 0.07	1.34 ± 0.06	.01	<.01
90	1.67 ± 0.04	1.58 ± 0.05	1.58 ± 0.03	.23	.13
CRP level, mg/dL					
0	43.33 ± 7.44	56.37 ± 9.81	52.34 ± 6.74	.29	.37
15	0.78 ± 0.20	2.36 ± 0.50	6.04 ± 1.30	<.01	<.01
30	0.65 ± 0.27	1.17 ± 0.77	4.60 ± 2.10	.53	.07
90	0.15 ± 0.03	0.45 ± 0.19	3.01 ± 1.50	.13	.06
ESR, mm/h					
0	82.98 ± 4.58	93.33 ± 5.62	77.87 ± 4.50	.16	.43
15	33.80 ± 1.95	56.13 ± 7.64	51.60 ± 3.00	<.01	<.01
30	25.60 ± 1.48	38.13 ± 4.27	37.20 ± 2.90	<.01	<.01
90	24.20 ± 2.16	26.33 ± 2.42	28.70 ± 2.0	.50	.13

NOTE. Data are mean ± SE, unless otherwise indicated. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ND, not done.

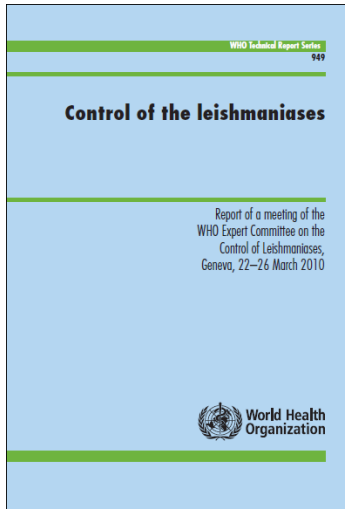
[a] Patients with VL who received 2 doses of a lipid formulation of amphotericin B (AmBisome; Gilead Sciences), 10 mg/kg each.

[b] Patients with VL who received 5 doses of a lipid formulation of amphotericin B (AmBisome), 4 mg/kg each.

[c] Patients with VL who received 30 doses of meglumine antimoniate (Glucantime; Rhone-Poulenc Rorer), 20 mg/kg each.

Traitement des leishmanioses en France : proposition d'un référentiel consensuel

Pierre A. Buffet[1,6,10], Éric Rosenthal[2,10], Jean-Pierre Gangneux[3], Edward Lightburne[4], Pierre Couppié[5], Gloria Morizot[6], Laurence Lachaud[7], Pierre Marty[8], Jean-Pierre Dedet[9]



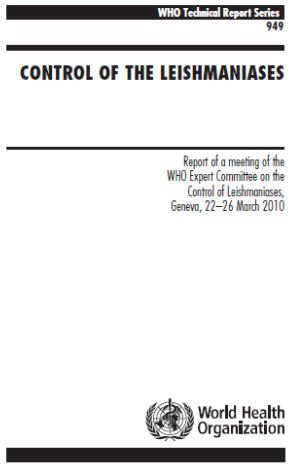


Tableau 1. Indications thérapeutiques dans la leishmaniose viscérale (OMS 2010)

Terrain	Espèce	Région	Traitements de 1ère ligne
Patient Immuno-compétent	*L. donovani*	Afrique de l'Est	antimoine pentavalent 20 mg Sbv/kg/j x 17 jours + paromomycine 11 mg(1)/kg/j x 17 jours
			amphotéricine B liposomale 30 mg/kg en 6-10 perfusions
			antimoine pentavalent 20 mg Sbv/kg/j x 30 jours
			amphotéricine B déoxycholate 0,75 - 1 mg/kg/j x 15-20 jours
			miltéfosine orale 150 mg/j (3) x 28 jours
		Asie	amphotéricine B liposomale 10 mg/kg en 1-3 perfusions
			amphotéricine B liposomale 5 mg/kg dose unique + miltéfosine orale 150 mg/j x 7 j
			amphotéricine B liposomale 5 mg/kg dose unique + paromomycine 11 mg/kg/j x 10 j
			paromomycine 11 mg/kg/j x 10 j + miltéfosine orale 150 mg/j x 10 j
			amphotéricine B déoxycholate 0,75 - 1 mg/kg/j x 15-20 jours
			miltéfosine orale 150 mg/j (3) x 28 jours
			paromomycine 11 mg/kg/j x 21 j
			antimoine pentavalent 20 mg Sbv/kg/j x 30 jours (3)
	L. infantum	Europe du Sud Afrique Asie Amériques	Antimoine pentavalent 20 mg Sbv/kg/j x 28 jours
			amphotéricine B liposomale 18-21 mg/kg(1) en 2-6 perfusions
			amphotéricine B déoxycholate 0,75 - 1 mg/kg/j x 30 jours
Patient immuno-déprimé			amphotéricine B liposomale 30-40 mg/kg en 4-10 perfusions
			amphotéricine B déoxycholate 1 mg/kg/j x 30 jours

+ prophylaxie secondaire ?

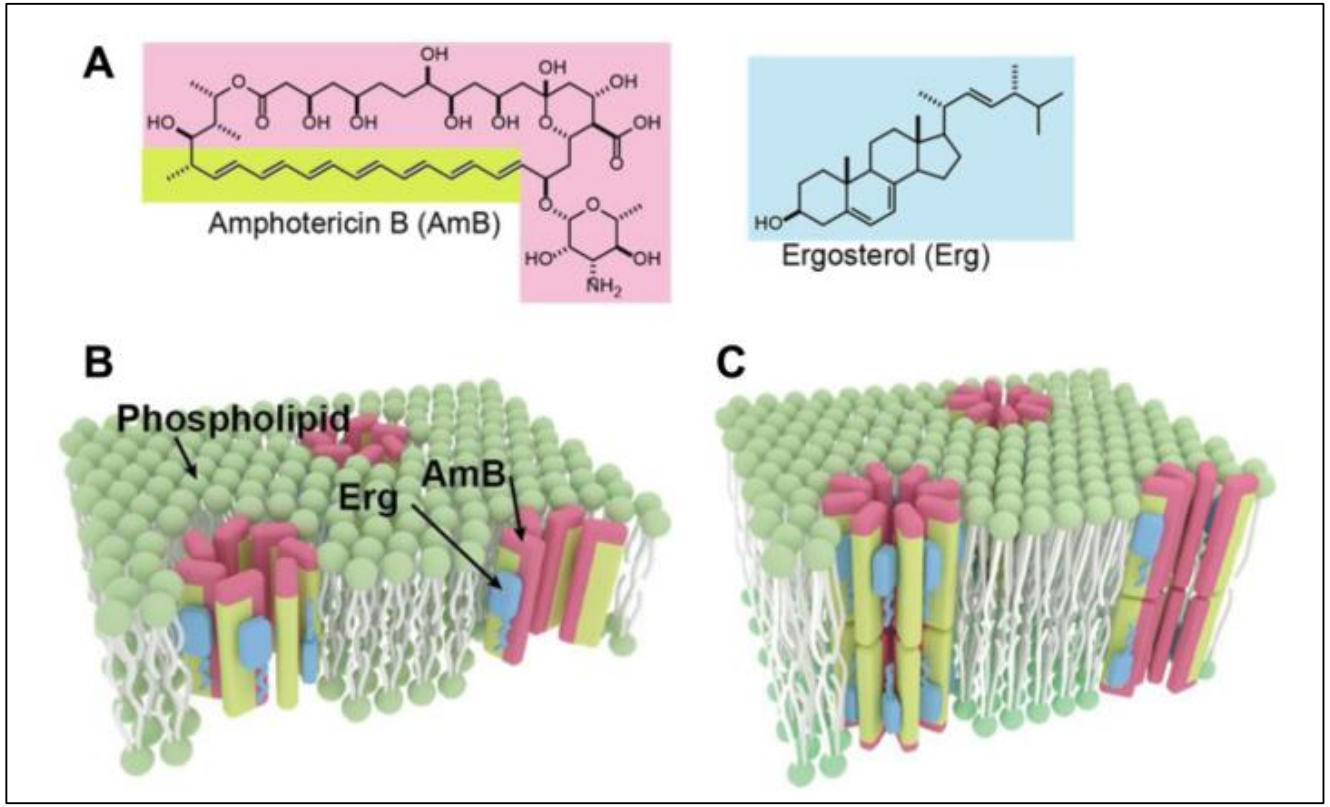
(1) Glucantime, Pentostam et générique (2) Soit 15 mg de base (3) sauf au Bihar

Traitement (Référentiel français Nov 2008)

Presse Med 2011

- amphotéricine B liposomale (AmBisome°)
- Enfant: 10 mg/kg J1 & J2 perfusion lente (?)
- Adulte: 3 mg/kg J1-J5, J10 (schéma court à évaluer)
- Dose plus élevée chez l'immunodéprimé (40-60 mg/kg)
- Suivi clinique + NFS (PCR quantitative chez l'immunodéprimé)

Rechute chez les patients immunodéprimés (Antinori et al, 2008) (Lachaud et al, 2009)



Structures of AmB ion channel assemblies (Umegawa Y, et al, 2022)

La partie de polyenes (lipophile) de la molécule macrocyclique interagit avec l'ergostérol de la bicouche lipidique et forment des pores laissant sortir les ions et les petites molécules; assemblage de 7 molécules d'AmB (possiblement 6 ou 8) (Umegawa Y, et al, 2022)

Table 1. Characterization of *Leishmania infantum* strains isolated from HIV-1–infected patients with multiple episodes of visceral leishmaniasis.

Patient, strain	Date of isolation	PFGE profile	IC_{50}, mean µg/mL ± SD	
			Promastigotes	Amastigotes[a]
Patient 1				
3049	May 1995	A	0.39 ± 0.01	0.46 ± 0.05
3110	Nov 1995	A	0.48 ± 0.01	…
4054	Sep 2000	A	0.40 ± 0.03	…
5159	Dec 2005	A	0.42 ± 0.01	0.34 ± 0.14
Patient 2				
3476	Sep 1997	B	0.39 ± 0.01	0.56 ± 0.12
4147	Feb 2001	B	0.40 ± 0.03	0.69 ± 0.08
Patient 3				
3320	Jan 1997	C	0.39 ± 0.02	…
3842	Jul 1999	C	0.40 ± 0.02	…
Patient 4				
3135	Dec 1995	D	0.62 ± 0.06	…
3256	Jun 1996	D	0.29 ± 0.02	…
Patient 5				
4038	Jun 2000	E	0.40 ± 0.03	…
4340	Jan 2002	E	0.60 ± 0.02	…

Characterization of Leishmania infantum strains isolated from HIV-1-infected patients with multiple episodes of visceral leishmaniasis (Lachaud et al, 2009)

Rechute chez les patients immunodéprimés (Antinori et al, 2008) (Lachaud et al, 2009)

Patients immunodéprimés => rechutes, parfois multiples après traitement par AmB liposomale :

- 46-60% chez les patients séropositifs pour le VIH
- 24% pour les patients TOS (8% rechutes multiples)

LV multi-récidivantes dues à la même souche de parasite initiale (non à des réinfections)

Etude *in vitro* de la sensibilité de ces souches :

→ Valeurs de concentration inhibitrice médiane (IC50) stables au fil des rechutes

→ **résistance non conventionnelle probable à l'AmB (analogie avec le comportement de *Plasmodium falciparum et dérivés de l'artémisinine*)**

Pour le paludisme, IC50 directement ex-vivo, donc sur de potentiels résistants

Pour la leishmaniose besoin de mise en culture, donc IC50 réalisée (potentiellement) sur des parasites sensibles, les « résistants » en état fitness cost (duplication lente)

(Lachaud et al, 2009)

PLOS | NEGLECTED TROPICAL DISEASES

2015

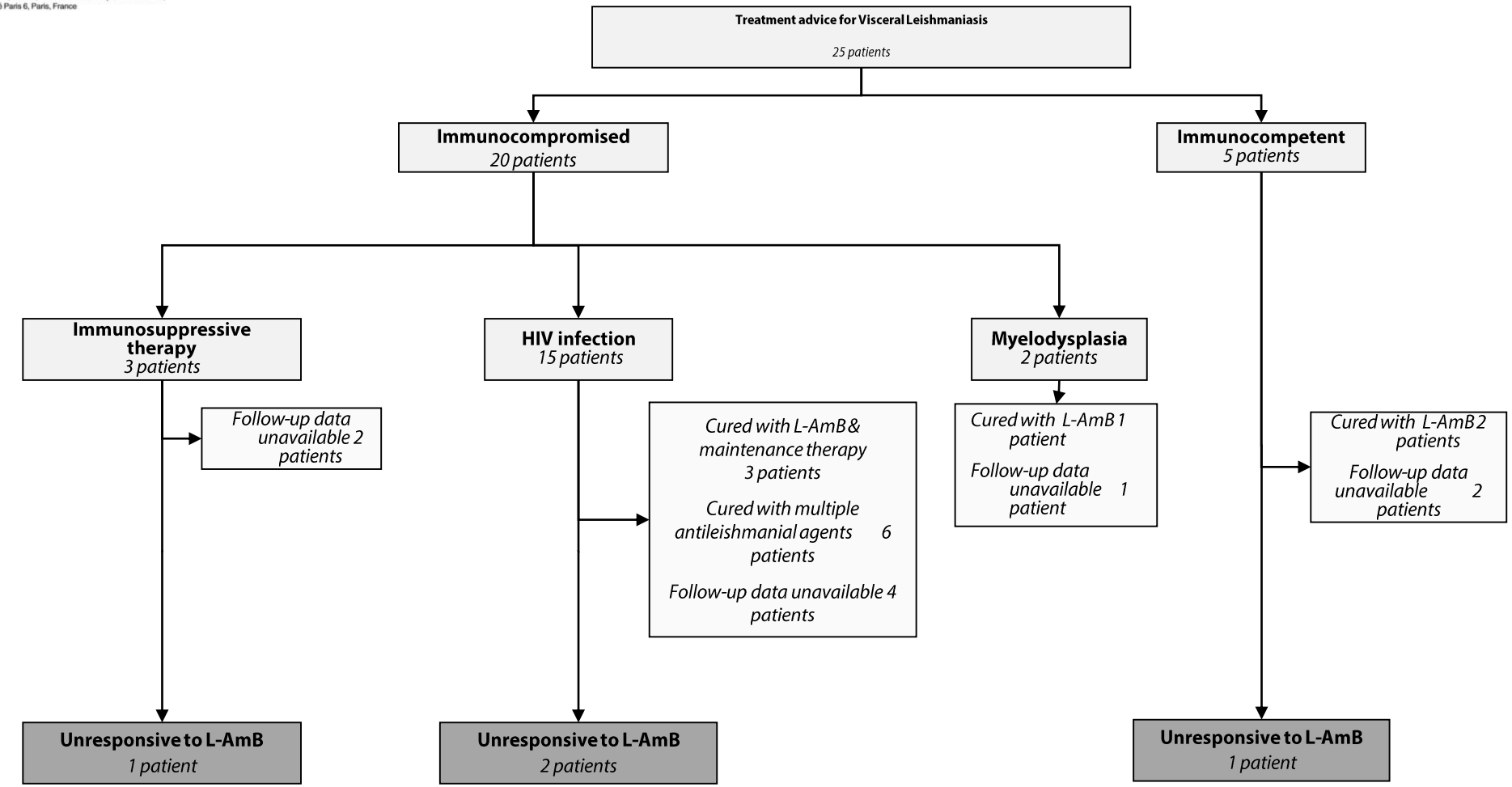
RESEARCH ARTICLE

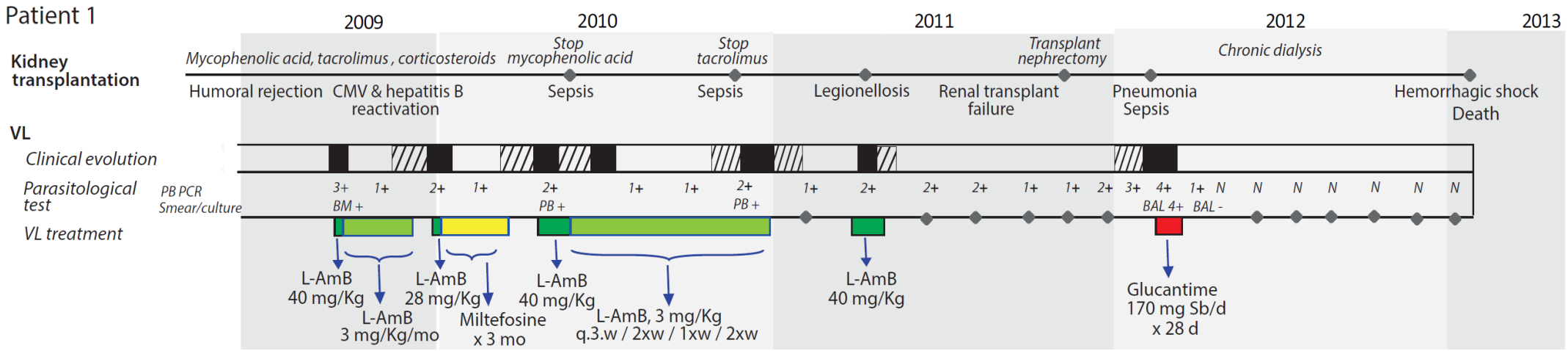
Antimony to Cure Visceral Leishmaniasis Unresponsive to Liposomal Amphotericin B

Gloria Morizot[1], Romain Jouffroy[2], Albert Faye[3], Paul Chabert[4], Katia Belhouari[5], Ruxandra Calin[5], Caroline Charlier[6], Patrick Miailhes[4], Jean-Yves Siriez[7], Oussama Mouri[8], Hélène Yera[9], Jacques Gilquin[6], Roland Tubiana[5], Fanny Lanternier[6], Marie-France Mamzer[10], Christophe Legendre[10], Dominique Peyramond[4], Eric Caumes[5], Olivier Lortholary[6], Pierre Buffet[6,11]*

1 Plateforme ICAReB, Institut Pasteur, Paris, France, **2** Service d'anesthésie-réanimation, Hôpital Necker, Paris, France, **3** Service de Pédiatrie générale, Hôpital Robert Debré, Paris, France, **4** Service de Maladies Infectieuses et Tropicales, Hôpital de la Croix-Rousse, Lyon, France, **5** Service de Maladies Infectieuses et Tropicales, Hôpital Pitié-Salpêtrière, Université Pierre et Marie Curie, Paris, France, **6** Université Paris Descartes, Centre d'Infectiologie Necker-Pasteur, Hôpital Necker-Enfants malades, IHU Imagine, Paris, France, **7** Service d'Accueil des Urgences pédiatriques, Hôpital Robert Debré, Paris, France, **8** Service de Parasitologie-Mycologie, Hôpital Pitié-Salpêtrière, Paris, France, **9** Service de Parasitologie-Mycologie. Hôpital Cochin, Faculté de Médecine, Paris Descartes, Paris, France, **10** Service de transplantation rénale, Hôpital Necker, Paris, France, **11** 945 INSERM, Université Paris 6, Paris, France

* pabuffet@gmail.com





Retour aux dérivés pentavalents de l'antimoine
Une option en cas de non réponse avérée à l'amphotéricine B liposomale ?

Cas général du patient immunodéprimé:

Commencer par une cure pleine d'AmBisome d'au moins 40 mg/kg cumulés

Réserver la miltéfosine pour prophylaxie secondaire sur situation contrôlée
(charge parasitaire circulante faible ou nulle)

En cas de rechutes multiples traitement d'attaque choisi en fonction des traitement antérieurs, de la suspicion de non-réponse à l'AmBisome, des atteintes d'organe et des profils de toxicité

Clinical Infectious Diseases
IDSA GUIDELINE
Clinical Infectious Diseases® 2016;63(12):e202–64

Diagnosis and Treatment of Leishmaniasis: Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH)

Naomi Aronson,[1] Barbara L. Herwaldt,[2] Michael Libman,[3] Richard Pearson,[4] Rogelio Lopez-Velez,[5] Peter Weina,[6] Edgar M. Carvalho,[7] Moshe Ephros,[8] Selma Jeronimo,[9] and Alan Magill[10]

Visceral leishmaniasis[f]								
VL	Treatment of choice	Liposomal amphotericin B[g]	AmBisome	Astellas	IV	FDA-approved regimen, if immunocompetent[f,h]: 3 mg/kg/day on days 1–5, 14, and 21 (total dose 21 mg/kg) FDA-approved regimen, if immunosuppressed[i]: 4 mg/kg/day on days 1–5, 10, 17, 24, 31, and 38 (total dose 40 mg/kg)	Yes, for this indication	See XIX regarding other regimens that have been used in various settings. Fo treatment of VL in immunocompetent[h] person with VL acquired in East Africa, regimens with total doses ≥40 mg/kg may be needed.
	Alternatives[l]							
VL		Miltefosine[k]	Impavido	In US: Knight Therapeutics, via Profounda, the US marketer. In Canada: via Special Access Program	Oral	FDA-approved regimen: if 30–44 kg, 50 mg bid for 28 d; if ≥45 kg, 50 mg tid for 28 d[i]	Yes, for VL caused by *L. donovani*	On the basis of anecdotal experience in Europe and Brazil, not as effective for V caused by *L. infantum-chagasi*. In general, target dose is ~2.5 mg/kg/day, but doses >150 mg/day have nc been studied. GI side effect may limit higher doses. See Table 4 and XXVI.
		Pentavalent antimonials[d,l]						
VL		Sodium stibogluconate	Pentostam	~~GlaxoSmithKline, via CDC Drug Service or USAMMDA for military healthcare beneficiaries[e]~~ Via Special Access Program in Canada	IV, IM (IV preferred in North America[a])	20 mg Sb^V/kg/day for 28 d[i]	No; but available in the US under a CDC-sponsored IND protocol. For military healthcare beneficiaries, available from USAMMDA.[e] In Canada, via Special Access Program	Supplied as 100 mg Sb^V/mL. Dilute dose in D5W (~50–100 mL) for IV, ~10–30-minute infusion. Use of an i line filter is recommended.
VL		Meglumine antimoniate	Glucantime	Sanofi Via Special Access Program in Canada	IV, IM (IV preferred in North America[a])	As per Pentostam	No; in US, would require investigator-sponsored IND protocol. In Canada, via Special Access Program	Supplied as 81 mg Sb^V/mL. Dilute dose in D5W (~50–100 mL) for IV, ~10–30-minute infusion.
VL		Amphotericin B deoxycholate[g]	Fungizone	Bristol-Myers Squibb	IV	1 mg/kg per dose daily or every other day for a total of 15–20 doses[i]	Yes, but not for VL; off-label use	
VL		Amphotericin B lipid complex	Abelcet	Sigma-Tau Pharmaceuticals	IV	Immunocompetent[f,h]: 2–3 mg/kg/day for 5–10 d Immunosuppressed[i]: 3–5 mg/kg/day for 10 d[m]	Yes, but not for VL; off-label use	L-AmB is the treatment of choice for VL. Bioequivalence between ABLC and L-AmB for treatment of VL has not been established; ABLC has been less well studied in VL treatment trials and, anecdotally, may not be as effective as AmBisome (rough conversion: 3 mg/kg of liposomal amphotericin B is about 5 mg/kg of ABLC).
VL	Lesser alternative	Pentamidine isethionate	Pentam 300	APP Pharmaceuticals	IV, IM (IV preferred in North America[a])	4 mg/kg every other day or 3 times per week for ~15–30 doses[i]	Yes, but not for VL; off-label use	Considered second-line therapy because of toxicity (see Table 4) and lower efficacy.

Traitement des leishmanioses en France : proposition d'un référentiel consensuel

Presse Med. 2010; □□: □□□

Pierre A. Buffet[1], Éric Rosenthal[2]*, Jean-Pierre Gangneux[3], Edward Lightburne[4], Pierre Couppié[5], Gloria Morizot[6], Laurence Lachaud[7], Pierre Marty[8], Jean-Pierre Dedet[9]

- **Antimoniaux pentavalents** (Stibogluconate de Sodium et antimoniate de méglumine)
  → Conversion intracellulaire en antimoine trivalent et inhibition la topoisomérase I de l'ADN provoquant la mort du parasite; effets secondaires : cardiomyopathie et insuffisance rénale

- **Paromomycine** (antibiotique aminoglycoside)
  → Se lie aux ribosomes des parasites et inhibe leur synthèse protéique; effet secondaire : ototoxicité

- **Pentamidine**
  → Perturbe la réplication de l'ADN de *Leishmania;* effets secondaires : hypoglycémie et néphrotoxicité

- **Miltefosine** (seul par voie orale)
  → Perturbe la membrane cellulaire du parasite et déclenche l'apoptose; effet secondaire : tératogénicité

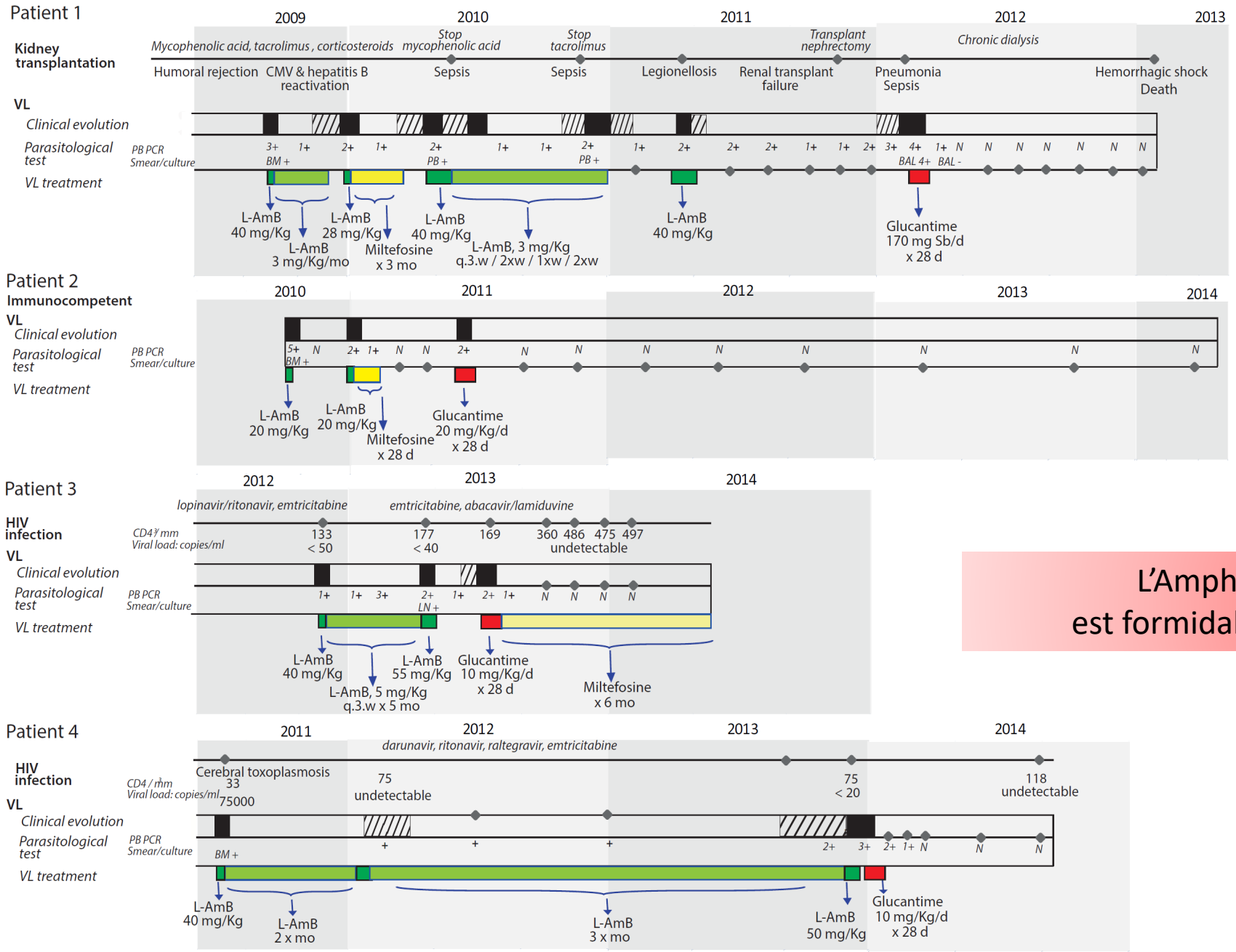
- **Amphotéricine B**
  → Cible les membranes et provoque la lyse des parasites (la forme liposomale de l'AmB améliore sa tolérance et réduit sa toxicité)

- Nouvelles « all-new, all-oral drugs » par DNDi (Drugs for Neglected Diseases initiative) et leurs partenaires (Novartis, GSK Global Health Unit, Drug Discovery Unit,,,) en différentes phases de tests : LXE408, GSK245, DNDi-6899, DNDi-6174

TABLEAU I

Anti-leishmaniens utilisables en France et principaux effets secondaires en cas d'administration systémique

Famille	Molécule	Spécialité	Cible d'action	Principaux effets secondaires[a]
Polyène	Amphotéricine B désoxycholate	Fungizone®	Altération membranaire par fixation à l'ergostérol	Toxocité rénale (Fungizone® >> AmBisome®), hypokaliémie, fièvre, frissons, nausées, vomissements
	Amphotéricine B liposomale	AmBisome®		
Dérivé pentavalent de l'antimoine	Antimoniate de méglumine	Glucantime®	Synthèse de l'ATP lors des métabolismes bioénergétiques (glycolyse, métabolisme des acides gras)	Toxicités cardiaque, hématologique, hépatique et rénale, asthénie, anorexie, céphalées, nausées, vomissements, myalgies, arthralgies, DRESS[b]
Hexadecyl-phosphocholine[a]	Miltéfosine	Impavido®	Cytostatique	Tératogénicité, diarrhées (50 % des cas), nausées, vomissements, intolérances rénale ou hépatique
Diamidine	Iséthionate de pentamidine	Pentacarinat®	Synthèse de l'ADN	Toxicités rénale et hématologique, troubles du métabolisme glucidique (hypoglycémie jusqu'au diabète définitif) et troubles électrocardiographiques
Azole	Fluconazole	Triflucan®	Synthèse de l'ergostérol	Bonne tolérance générale, nausées, flatulences, douleurs abdominales, diarrhées, rashs
Anti-ischémique et anti-TNF	Pentoxifylline	Torental®	Anti-TNFα	Troubles digestifs (rares) Allergie, *flush*, hypotension



L'Amphotéricine B liposomale
est formidable mais ne résout pas tout

VL episode; ▨ olygosymptomatic VL; BM: bone marrow; PB: peripheral blood; LN: lymph node;
quantitative PCR (N = negative; 1+ = 0.5-10; 2+ = 11-100; 3+ = 101-1000; 4+ = 1 001-100 000; 5+ >100 000 parasites/ml); BAL: broncho-alveolar lavage; q.3.w: every 3 weeks; xw: per week

Prévention 2aire de la LV - ID

Dias Emmanuel Lafond

VIH+

Relapse
VIH+ 46-60%
VIH- 8-24%

VIH-

55. We recommend administering secondary prophylaxis (chronic maintenance therapy) to decrease the risk for post-treatment relapse of VL in persons with HIV/AIDS-associated immunosuppression (eg, CD4 T-lymphocyte counts <200 cells/mm^3) *(strong, moderate)*.

56. Persons with VL and HIV/AIDS coinfection should be monitored indefinitely (until effective immune reconstitution) for evidence of posttreatment relapse; ART and secondary prophylaxis provide only partial protection against relapse. Antileishmanial treatment is indicated for persons who have clinical and parasitologic evidence of recurrence *(strong, low)*.

72. Secondary prophylaxis is not recommended for initial management in persons with VL who have not manifested a relapse *(weak, low)*. Comment: Immunosuppressed persons with VL who are not coinfected with HIV typically have higher response rates to initial treatment and lower recurrence rates than HIV-coinfected persons.

75. Immunosuppressed persons with VL who are not coinfected with HIV should be monitored for a minimum of 1 year (ideally lifelong or until effective immune reconstitution) to assess for posttreatment relapse. During clinical follow-up, assess for symptoms and, if present, pursue parasitologic confirmation of relapse *(strong, very low)*.

Diagnosis and Treatment of Leishmaniasis: Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). Am J Trop Med Hyg. 2017;96(1):24-45

ORIGINAL ARTICLE TROPICAL AND PARASITIC DISEASES

Tumor necrosis factor alpha antagonist drugs and leishmaniasis in Europe

P. Zanger[1], I. Kötter[2], P. G. Kremsner[1] and S. Gabrysch[3]

1) Institut für Tropenmedizin, Eberhard Karls Universität, Wilhelmstraße, 2) Medizinische Klinik, Eberhard Karls Universität, Otfried-Müller-Straße, Tübingen and 3) Institut für Public Health, Ruprecht Karls Universität, Im Neuenheimer Feld, Heidelberg, Germany

Clin Microbiol Infect

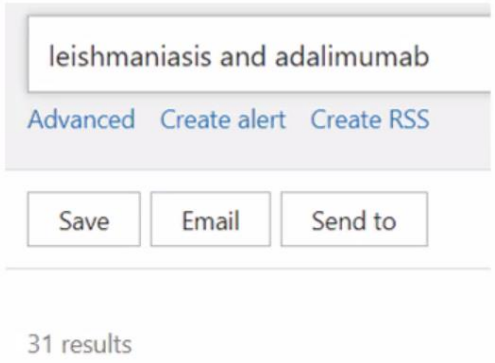
Dias Emmanuel Lafond

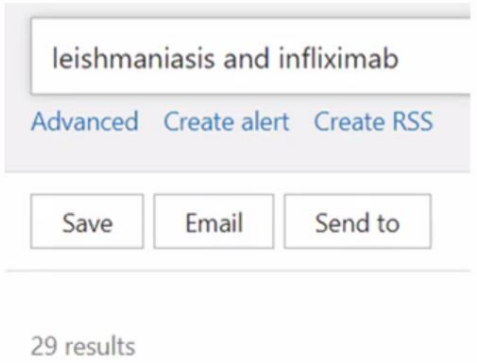
- Analyse des cas publiés de leishmaniose-aTNF en Europe 2006-2010
- N=19
- 14 cas autochtones, 3 Algérie, 1 Erythrée
- Médiane 18 mois entre début aTNF – diagnostic leishmaniose
- Parmis les cas = Ada/infli vs etanercept 16/1
- En Europe les prescription = Ada/infli vs etanercept 2/1

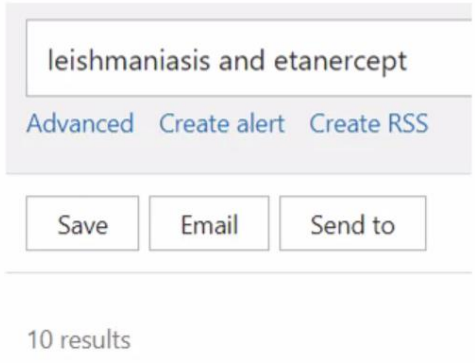
Risque de Leishmaniose x8 sous infli /ada vs etanercept

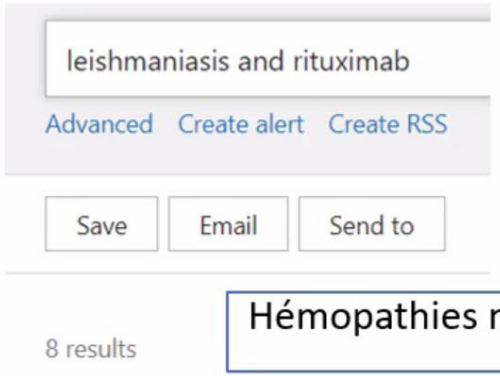
Dias Emmanuel Lafond

Drug-induced LV

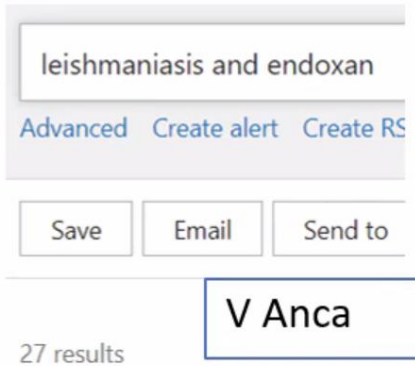




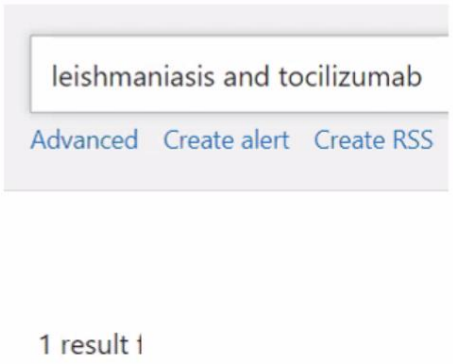




Hémopathies malignes



V Anca



Dias Emmanuel Lafond

SURVEILLANCE AND OUTBREAK REPORTS

Re-emergence of leishmaniasis in Spain: community outbreak in Madrid, Spain, 2009 to 2012

A Arce (araceli.arce@salud.madrid.org)[1], A Estirado[1], M Ordobas[1], S Sevilla[1], N García[1], L Moratilla[1], S de la Fuente[2], A M Martínez2, A M Pérez[1], E Aránguez[2], A Iriso[2], O Sevillano[2], J Bernal[2], F Vilas[2]

1. Division of Epidemiology, Health Promotion and Prevention Subdirectorate, Primary Care Directorate, Madrid, Spain
2. Division of Health Environmental, Ordination and Inspection Directorate, Health Department, Madrid, Spain

Citation style for this article:
Arce A, Estirado A, Ordobas M, Sevilla S, García N, Moratilla L, de la Fuente S, Martínez AM, Pérez AM, Aránguez E, Iriso A, Sevillano O, Bernal J, Vilas F. Re-emergence of leishmaniasis in Spain: community outbreak in Madrid, Spain, 2009 to 2012. Euro Surveill. 2013;18(30):pii=20546. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20546

Article submitted on 24 August 2012 / published on 25 July 2013

TABLE

Clinical and epidemiological characteristics of leishmaniasis cases by clinical presentation, community outbreak in the region of Madrid, Spain, July 2009–December 2012 (n=446)

Characteristic	Visceral forms	Cutaneous forms	Total
	Number of cases (%)[a]	Number of cases (%)[a]	Number of cases (%)
Total	**160 (35.9)**	**286 (64.1)**	**446 (100.0)**
Sex			
Male	117 (73.1)	155 (54.2)	272 (61.0)
Female	43 (26.9)	131 (45.8)	174 (39.0)
Age in years			
<2	18 (11.2)	5 (1.7)	23 (5.2)
2–14	12 (7.5)	28 (9.8)	40 (9.0)
15–29	19 (11.9)	20 (7.0)	39 (8.7)
30–44	35 (21.9)	52 (18.2)	87 (19.5)
45–59	40 (25.0)	117 (40.9)	157 (35.2)
≥60	36 (22.5)	64 (22.4)	100 (22.4)
Country of origin			
Spain	116 (72.5)	262 (91.6)	378 (84.8)
Sub-Saharan Africa	32 (20.0)	4 (1.4)	36 (8.1)
Other countries	12 (7.5)	20 (7.0)	32 (7.2)
Year the symptoms started			
2009	3 (1.9)	3 (1.0)	6 (1.3)
2010	31 (19.4)	66 (23.1)	97 (21.8)
2011	70 (43.7)	126 (44.1)	196 (43.9)
2012	56 (35.0)	91 (31.8)	147 (33.0)
Classification			
Confirmed	137 (85.6)	284 (99.3)	421 (94.4)
Probable	23 (14.4)	2 (0.7)	25 (5.6)
Diagnosis method			
Biopsy/aspirate	126 (78.8)	283 (99.0)	409 (91.7)
Culture	13 (8.1)	23 (8.0)	36 (8.1)
Serology	100 (62.5)	0 (0.0)	100 (22.4)
Hospitalisation			
Admitted to hospital	135 (84.4)	1 (0.3)	136 (30.5)
Intrinsic risk factors			
All	50 (31.3)	18 (6.3)	68 (15.2)
Immunosuppressive treatment	25 (15.6)	13 (4.5)	38 (8.5)
HIV infection	16 (10.0)	2 (0.7)	18 (4.0)
Other immunosuppressive conditions	20 (12.5)	6 (2.1)	26 (5.8)
Alcoholism	13 (8.1)	3 (1.0)	16 (3.6)
Drug injection	1 (0.6)	1 (0.3)	2 (0.4)
Extrinsic risk factors[b]			
Contact with dogs	52 (32.5)	62 (21.7)	114 (25.6)
Contact with sick dogs	7 (4.4)	10 (3.5)	17 (3.8)
Presence of mosquitoes[c]	27 (16.9)	62 (21.7)	89 (20.0)
Waste and rubbish dumps	6 (3.8)	10 (3.5)	16 (3.6)
Walks near livestock farms	5 (3.1)	9 (3.1)	14 (3.1)
Travel history during the incubation period			
Travel to highly endemic areas	34 (21.3)	63 (22.0)	97 (21.7)

Leishmaniose

Viscérale

1. Maladie surtout européenne
2. PCR sang quantitative d'abord
3. **AmBisome 21 mg/kg cumulés**
4. Immunodéprimé 40-60 mg/kg cumulés et contrôler la charge (PCR négative) avant prophylaxie secondaire par AmBisome ou miltéfosine ou pentamidine ou antimoine ou paromomycine

N'hésitez pas à appeler ou écrire : 06 26 16 68 11 pierre.buffet@pasteur.fr clea.melenotte@aphp.fr

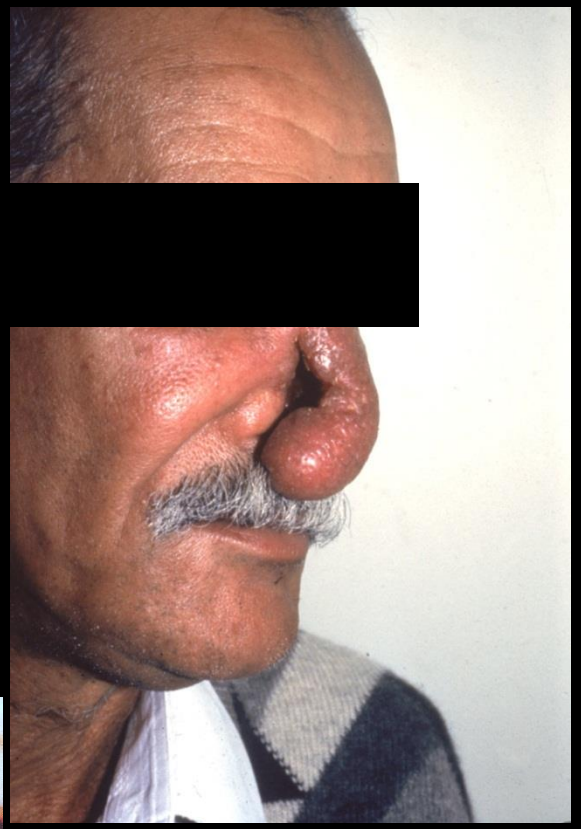
Traitement
Leishmaniose cutanée

Mucosal Leishmaniasis in Travelers with *Leishmania braziliensis* Complex Returning to Israel

Michal Solomon, Nadav Sahar, Felix Pavlotzky, Aviv Barzilai, Charles L. Jaffe, Abedelmajeed Nasereddin, Eli Schwartz

Enjeux : atteinte muqueuse ?

From Schaller



. Moins de 7% des cas en Amérique latine

. Rare avec L major et L tropica

. Fréquent avec L. infantum

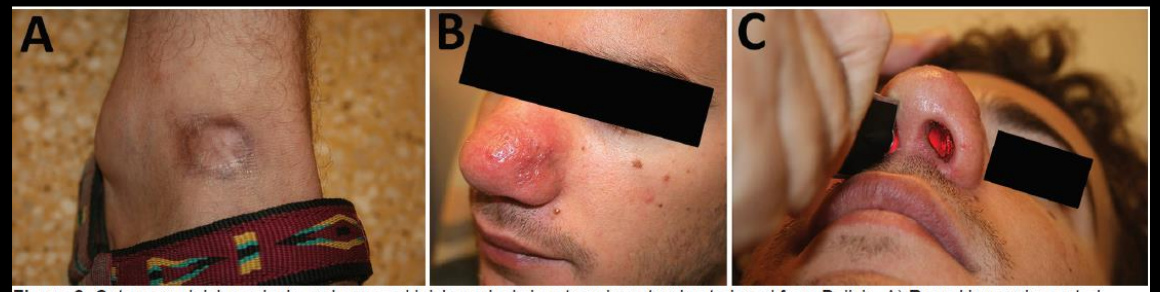


Figure 3. Cutaneous leishmaniasis and mucosal leishmaniasis in a traveler returning to Israel from Bolivia. A) Round hyperpigmented patch on the dorsum of right leg, representing old cutaneous leishmaniasis scar. B) Indurated erythematous patch of the nasal skin of the same patient appearing after 1 year. C) Illuminating in the right nostril sheds light into the left side, reflecting a hole within the nasal septum.

Mucosal Leishmaniasis in Travelers with *Leishmania braziliensis* Complex Returning to Israel

Michal Solomon, Nadav Sahar, Felix Pavlotzky, Aviv Barzilai, Charles L. Jaffe, Abedelmajeed Nasereddin, Eli Schwartz

Mucosal leishmaniasis (ML) is a complication of New World cutaneous leishmaniasis (CL) caused mainly by *Leishmania (Viannia) braziliensis*. This retrospective study investigated all cases of ML caused by *L. (V.) braziliensis* in a tertiary medical center in Israel, evaluating the risk factors, clinical presentations, diagnosis, treatment, and outcome of mucosal involvement in ML caused by *L. (V.) braziliensis* in travelers returning to Israel. During 1993–2015, a total of 145 New World CL cases were seen in travelers returning from Bolivia; among them, 17 (11.7%) developed ML. Nasopharyngeal symptoms developed 0–3 years (median 8 months) after exposure. The only significant risk factor for developing ML was the absence of previous systemic treatment. Among untreated patients, 41% developed ML, compared with only 3% of treated patients (p = 0.005). Systemic treatment for CL seems to be a protective factor against developing ML.

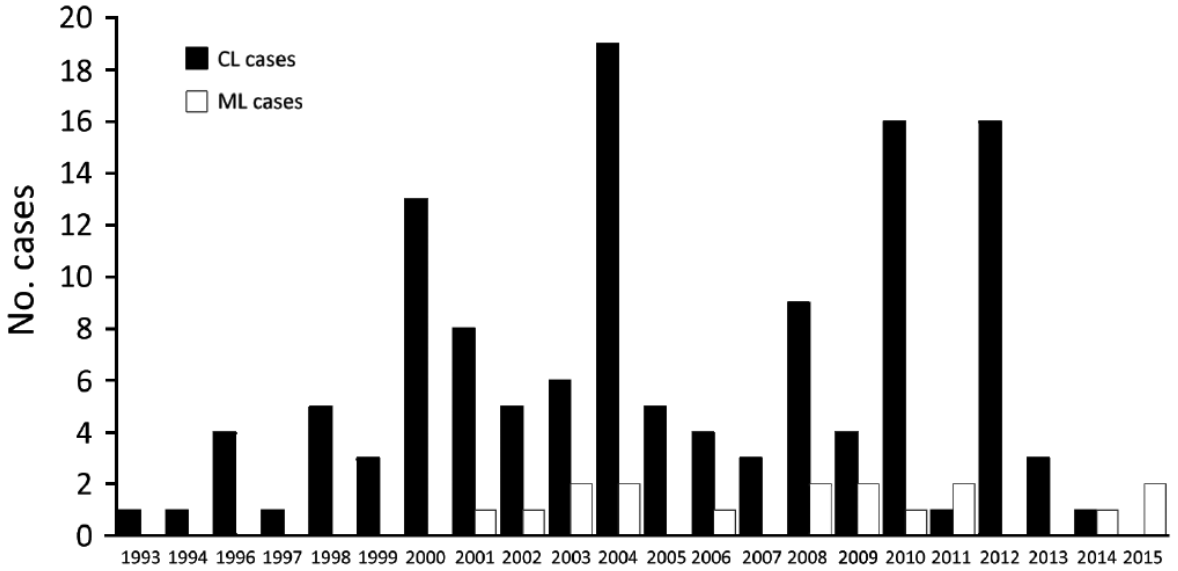


Figure 1. Number of CL and ML cases in Israel, 1993–2015. No cases were reported in 1995. CL, cutaneous leishmaniasis; ML, mucosal leishmaniasis.

Table 1. Comparison between patients with New World CL and those with ML, Israel, 1993–2015*

Characteristic	CL	ML
No. patients	128	17
Sex ratio, M:F	105:23 (82% male)	16:1 (94% male)
Mean age, y	24.2	27.6
Infected in Bolivia	83/100 (83%)	17/17(100%)
No. lesions	1.8	2.3
≥3 lesions	21/128 (16%)	5/17 (29%)
Lesion above waist	61/81 (75%)	9/17 (53%)
PCR positive	68/76 (89%)	15/17 (88%)

*Differences between categories were not significant. CL, cutaneous leishmaniasis; ML, mucosal leishmaniasis.

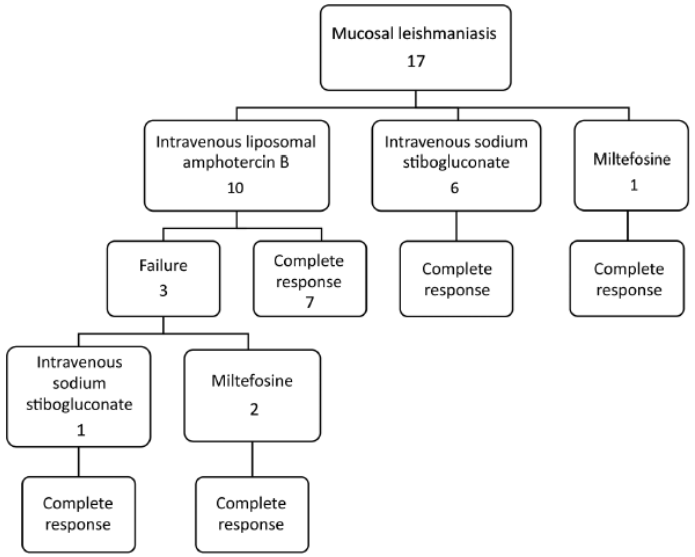


Figure 4. Treatment types and results for patients with mucosal leishmaniasis, Israel, 1993–2015.

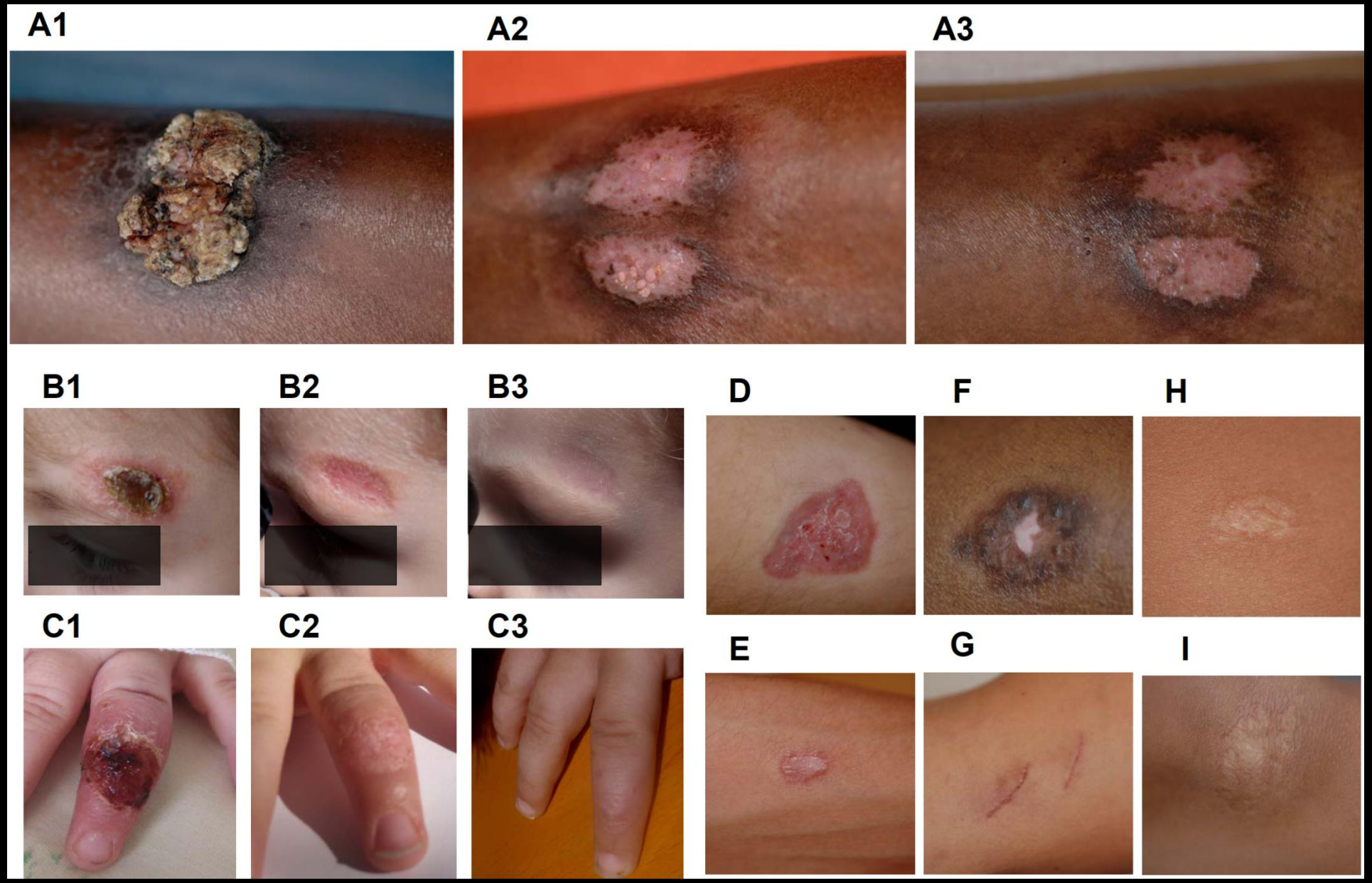
Table 2. Epidemiologic, clinical, and therapy data of patients with mucosal leishmaniasis, Israel, 1993–2015*

Patient no.	Age, y/ sex	No. primary lesions	Concurrent active CL	Location of primary lesions	Treatment				ML symptoms
					Primary cutaneous lesions	Mucosal lesions	After ML treatment failure	Response	
1	28/M	12	No	Trunk, upper extremities	None	IV SSG	No failure	CR	Oral ulceration, nasal obstruction
2	24/F	1	Yes	Lower extremities	Treated for concurrent CL	IV SSG	No failure	CR	Nasal obstruction
3	28/M	1	No	Lower extremities	None	IV L-AmB	No failure	CR	Nasal obstruction
4	28/M	1	No	Neck	IV SSG	IV L-AmB	No failure	CR	Nasal obstruction
5	26/M	1	No	Lower extremities	IV SSG	IV L-AmB	No failure	CR	Nasal obstruction
6	25/M	1	No	Face	IV SSG	IV L-AmB	No failure	CR	Oral ulceration
7	41/M	1	Yes	Lower extremities	Treated for concurrent CL	IV L-AmB	IV SSG	CL recurrence	Nasal obstruction, lacrimal gland obstruction
8	23/M	4	Yes	Neck, lower extremities	Treated for concurrent CL	IV L-AmB	No failure	None	Nasal obstruction, bone lesion
9	31/M	3	No	Upper and lower extremities	None	IV L-AmB	No failure	CR	Nasal obstruction, rhinorrhea
10	24/M	1	Yes	Upper extremities	Treated for concurrent CL	IV L-AmB	Miltefosine	CR	Nasal obstruction
11	41/M	0	No	No lesions†	None	Miltefosine	No failure	CR	Oral ulceration
12	25/M	1	NA	NA	None	IV SSG	No failure	CR	NA
13	22/M	2	No	NA	None	IV SSG	No failure	CR	Oral ulceration
14	25/M	3	No	Lower extremities	None	IV SSG	No failure	CR	NA
15	24/M	7	No	Face, upper extremities	None	IV SSG	No failure	CR	Oral ulceration, nasal obstruction
16	28/M	1	No	Upper extremities	None	IV L-AmB	No failure	CR	Nasal obstruction
17	23/M	2	No	Trunk	None	IV L-AmB	Miltefosine	CR	Nasal obstruction

*CL, cutaneous leishmaniasis; CR, complete response; IV L-AmB, intravenous liposomal amphotericin B; IV SSG, intravenous sodium stibogluconate; ML, mucosal leishmaniasis; NA, not available.
†Patient 11 had no primary cutaneous lesion.

Enjeux : impact social & délai de cicatrisation ?

Enjeu : aspect de la cicatrice ?


A1
A2
A3
B1
B2
B3
D
F
H
C1
C2
C3
E
G
I

Treat cutaneous leishmaniasis topically to reduce pain, risks & costs: why, who, how ?

Cléa Melenotte and Pierre Buffet
Hôpital Necker Enfants-Malades, APHP, Paris, France.; Université Paris-Cité, Paris, France.
Centre Médical, Institut Pasteur, Paris, France; Faculté de Médecine,

1. Why do we treat patients with cutaneous leishmaniasis?

1.1 To prevent complications?

Concomitant or delayed visceral or disseminated forms are very rare (< 1% in non immune travelers, *Guéry 21*)

Concomitant or delayed mucosal involvement is generally rare (2.7-5% of travelers in Western Europe, *Guéry 21* ; 41% of travelers in Israël returning mostly from Bolivia, *Solomon EID 19 ;* 1-15% in endemic areas, *Blum TMID 14*)

No treatment has demonstrated a preventive effect on mucosal spread

1.2 To improve scaring?

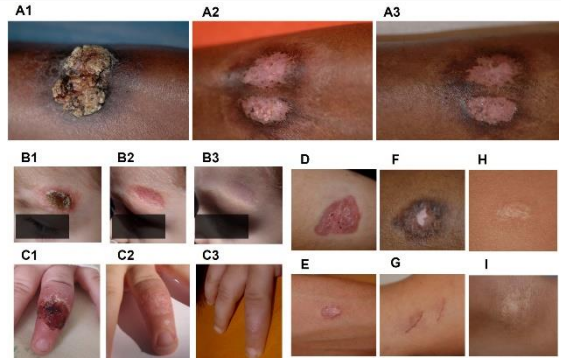
This is a desirable effect but so far no treatment has demonstrated a benefit in terms of long-term scaring

1.3 To reduce the impact of skin lesions?

This effect is proven but efficacy is on the duration of ulcerations or induration

From Guéry et al PLoS NTD 2021

	New World	Old World	p-value
	185 episodes	279 episodes	
Age, median [IQR]	30 [24-38]	32 [10-58]	0,81
Male	74.6% (138)	54.5% (152)	<0,01
Immunocompromised	0.6% (1/177)	8% (21/264)	<0,01
Type of tegumentary leishmaniasis			
Localized Cutaneous	96% (178)	94% (262)	
Muco-cutaneous	1.62% (3)	2.51% (7)	
Mucosal	1.08% (2)	2.51% (7)	
PKDL	0.54% (1)	0.36% (1)	
Disseminated cutaneous leishmaniasis	0.54% (1)	0.36% (1)	
Muco-cutaneous and visceral leishmaniasis	0% (0)	0.36% (1)	



2. How can we treat patients with leishmaniasis?

The risk of therapy should adapted to the impact of CL

2.1 Systemic options exist but are currently suboptimal

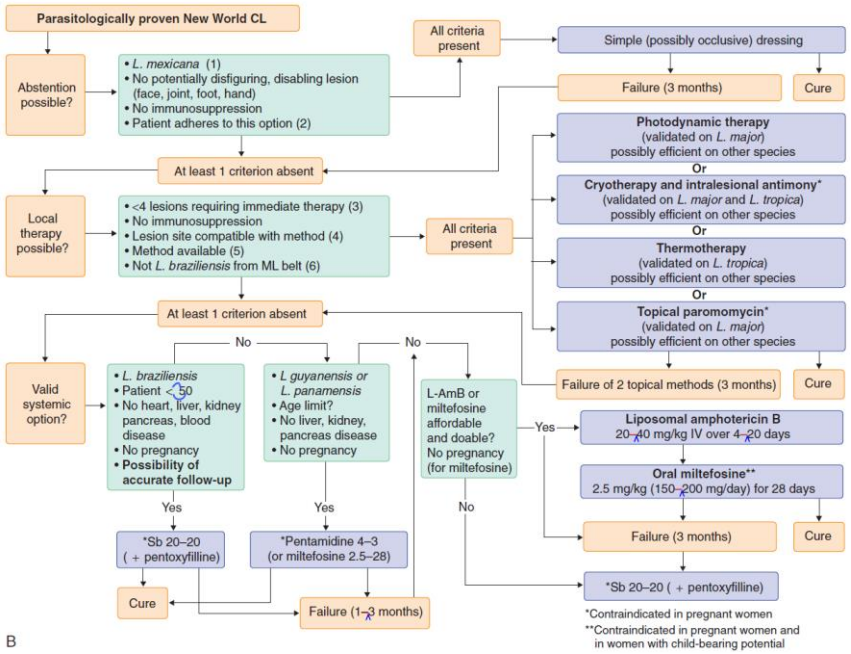
Antimony
Pentamidine
(Liposomal) amphotericin B
Miltefosine
because of poor applicability or questionable safety

2.2 Most local options use needles

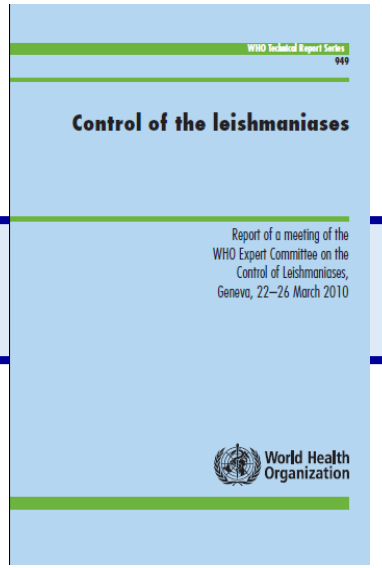
either for intralesional injections (antimony, pentamidine) or local anaesthesia (thermotherapy), & **expensive devices**

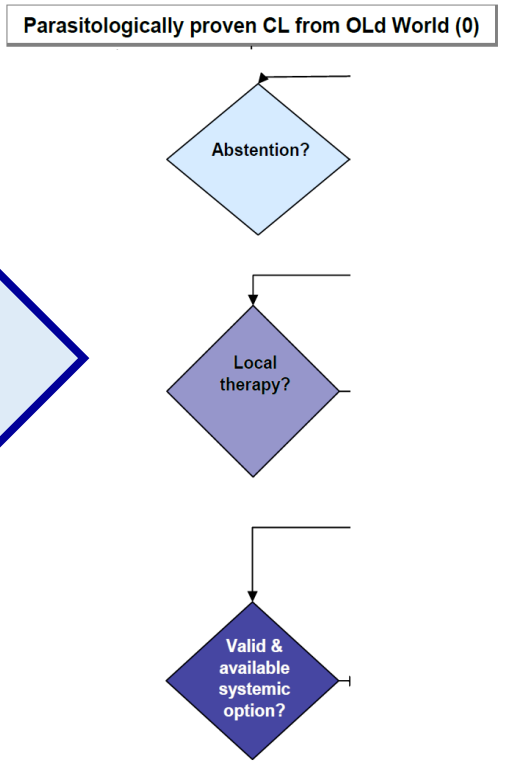
2.3 Local treatment with creams is almost painless, user-friendly, especially in children, and robustly validated by prospective trials *(Ben Salah 09, 13, Sousa 21)*

Reliable data and effective interactions to go from complex to simple algorithms



National Reference Centers & Programs





Clinical Infectious Diseases
IDSA GUIDELINE

Diagnosis and Treatment of Leishmaniasis: Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH)

Naomi Aronson,[1] Barbara L. Herwaldt,[2] Michael Libman,[3] Richard Pearson,[4] Rogelio Lopez-Velez,[5] Peter Weina,[6] Edgar M. Carvalho,[7] Moshe Ephros,[8] Selma Jeronimo,[9] and Alan Magill[10]

Clinical Infectious Diseases® 2016;63(12):e202–64

DOI: 10.1093/cid/ciw670

MAJOR ARTICLE

Travelers With Cutaneous Leishmaniasis Cured Without Systemic Therapy

G. Morizot,[1] E. Kendjo,[2] O. Mouri,[2] M. Thellier,[2] A. Pérignon,[3] F. Foulet,[5] F. Cordoliani,[6] E. Bourrat,[6,7] E. Laffitte,[8] I. Alcaraz,[9] N. Bodak,[10] C. Ravel,[4] M. Vray,[11] M. Grogl,[12] D. Mazier,[2] E. Caumes,[3] L. Lachaud,[4] P. A. Buffet,[1,2,13] and the Cutaneous Leishmaniasis French Study Group[a]

Clinical Infectious Diseases 2013;57(3):370–80

DOI: 10.1093/cid/cit269

Step-wise treatment decision in Cutaneous Leishmaniasis

Lesion(s) < 4 cm (papule, nodule or ulcerated nodule)

Situation 1

. *L major, L. mexicana* or self-curing lesion[1]
. No potentially disfiguring or disabling lesion (face, fingers, toes, ..)
. No uncontrolled diabetesor immunodepression
. Patient adheres to this option

All criteria above are present? → NO

YES

Wash lesion Wound dressing
Assure follow-up[2]

Cure ? → NO

YES

Situation 2

. < 4 lesions for which the patient asks for treatment[3]
. Not *L. braziliensis* from Peru or Bolivia
. No immunodepression
. Lesion site compatible with method[4]

All criteria above are present? → NO

YES

Cryotherapy + intralesional Sb[5]

Topical paromomycin[6]

Cure ? → NO

YES

Active lesion > 4 cm (Plaque)

Situation 3 [7]

. No cardiac or other major disease (liver kidney)
. Age < 55

All criteria above are present?

YES → **Systemic Sb**

NO → **Miltefosine[8]**

Cure ? → NO

YES

Entrée dans l'algorithme = diagnostic confirmé par PCR ou frottis cutané ou culture

Actualités sur le traitement de la leishmaniose. Romain Blaizot, Grégoire Pasquier, Philippe Picherit-Steinbrucker, Célia Rouges, Naïma Dahane, Christophe Ravel, Laurence Lachaud, Pierre Buffet, Cléa Melenotte*. In preparation*

1. Diagnostic

Faisabilité du traitement topique ?

Lésions cutanées sans atteinte muqueuse, (ni déjà présente, ni très probable[1])

Accord patient.e après information sur risque d'atteinte muqueuse secondaire

Pas d'atteinte disséminée (<11 lésions/<3 sites distants[2])

Bonne autonomie et observance prévisible

Localisation(s) compatible(s) avec application d'une crème sous pansement[3]

Grossesse en cours[4]

Tous critères présents

2. Traitement topique

Paromomycine crème[5]

Guérison

3. Traitement local

Cryothérapie superficielle + glucantime intra-lésionnel [7]

Guérison

Localisation compatible avec injections et nombre de lésions < 5

Crème paromomycine indisponible ou Echec[6]

Localisation incompatible avec injections [7] ou nombre de lésions > 4

Echec[6]

Toute autre situation : Patient immunodéprimé, forme disséminée, échec, grossesse, espèce rare, …

4.5 Discussion en RCP[13]

Echec

4. Traitement systémique

L. guyanensis très probable[8] Et Patient non observant Ou Refus du traitement topique

4.1 Pentamidine → Guérison

L. guyanensis très probable[8] Et Patient observant, sans CI[9]

4.2 Miltéfosine[9] → Guérison

L. infantum très probable[10] Et Patient immunodéprimé

4.3 AmB liposom. → Guérison

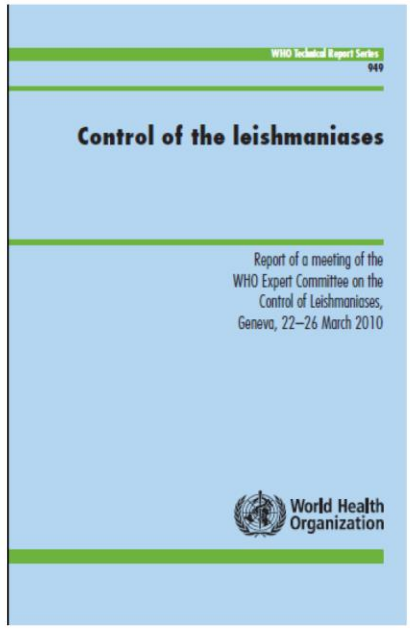
L. braziliensis très probable[11] Et Patient < 50 ans sans CI[12]

4.4 Glucantime IV → Guérison

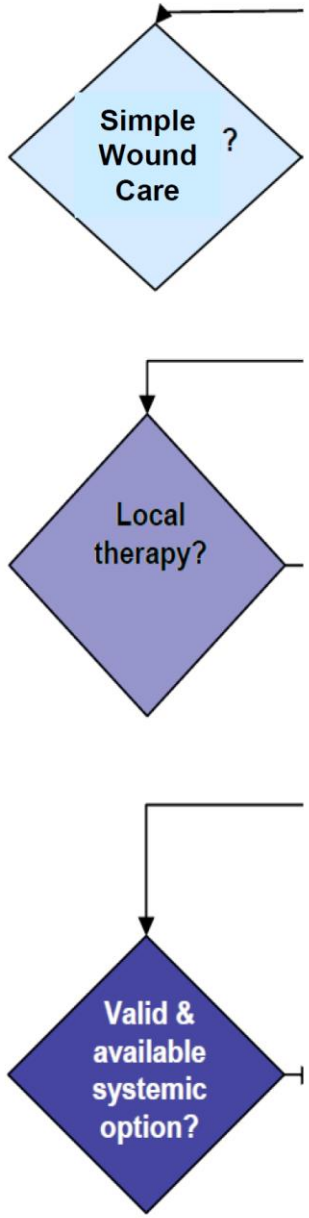
WHO Technical Report Series
949

CONTROL OF THE LEISHMANIASES

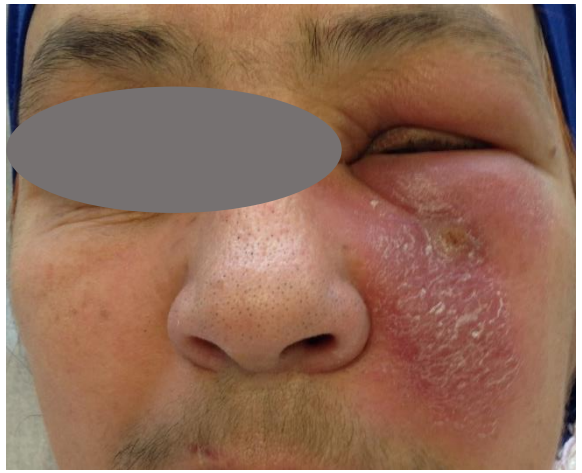
Report of a meeting of the
WHO Expert Committee on the
Control of Leishmaniases,
Geneva, 22–26 March 2010



Parasitologically proven CL from OLd World (0)



Simple clinical wisdom
&
Risk benefit analysis









Dr Lama Jalouk

Dr Lama Jalouk


PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Liposomal amphotericin B in travelers with cutaneous and muco-cutaneous leishmaniasis: Not a panacea

Citation: Guery R, Henry B, Martin-Blondel G, Rouzaud C, Cordoliani F, Harms G, et al. (2017) Liposomal amphotericin B in travelers with cutaneous and muco-cutaneous leishmaniasis: Not a panacea. PLoS Negl Trop Dis 11(11): e0006094. https://doi.org/10.1371/journal.pntd.0006094

Table 1. Main characteristics of 43 patients with tegumentary leishmaniasis treated with liposomal amphotericin B.

Characteristics of patients		n = 43
Demographics		
	Median age, years [range]	51 [1–86]
	Male	29 (67)
	Cardiovascular comorbidities and/or diabetes	7 (16)
	Immunocompromised subject	5 (12)
	Child	6 (14)
Clinical form		
	Localized cutaneous	32 (74)
	Mucocutaneous	8 (19)
	Disseminated cutaneous	2 (5)
	Localized cutaneous with visceral involvement	1 (2)
Area where infection was acquired		
	Old World	28 (65)
	New World	15 (35)
***Leishmania* Species (n = 35; 8 species unidentified)**		
	L. braziliensis	11 (31)
	L. braziliensis complex	2 (6)
	L. guyanensis	1 (3)
	L. amazonensis	1 (3)
	L. infantum	9 (26)
	L. major	6 (17)
	L. tropica	3 (8)
	L. donovani	2 (6)

L'Amphotéricine B liposomale
est formidable mais ne résout pas tout

Table 2. Predictors of success of liposomal amphotericin B in 41 patients with tegumentary leishmaniasis.

		Complete healing without relapse	Failure or relapse	Success of L-AmB	p value
		n = 19[a]	n = 22[a]	(%)	
Patients					
	Age	57 [2–80]	42 [1–86]	/	0.58
	Immunocompromised subject	2 (10)	3 (14)	40	0.99
	Localized cutaneous form	14 (74)	17 (77)	45	0.99
	Mucocutaneous form	4 (21)	3 (14)	57	0.68
	Frontline therapy with L-AmB	15 (79)	15 (68)	50	0.44
Country where infection was acquired					
	Old World	15 (79)	11 (50)	58	0.05
	New World	4 (21)	11 (50)	27	0.05
Leishmania species					
	Viannia subgenus	4 (21)	10 (45)	28	0.13
	L. infantum	7 (37)	2 (9)	78	0.06
	L. major	2 (10)	4 (18)	50	0.99
Clinical findings					
	Number of lesions	2 [1–30]	2 [1–8]	/	0.84
Treatment					
	Cumulative dose of L-AmB (mg/kg)	20 [6–40]	20 [16–56]	/	0.73

L-AmB, liposomal amphotericin B. Data are represented as n (%) or median [range] unless otherwise indicated.

[a]Two patients with improvement at first control visit (before day 90) but no subsequent follow-up were excluded from the analysis.

https://doi.org/10.1371/journal.pntd.0006094.t002

L'évolution diffère-t-elle en cas de traitement de traitement local ou systémique ?

	Traitement local N=107	Traitement systémique N=113	p
Taux de cicattrisation (Suivi > 41 jours) N (%)	95 (89)	97 (85)	0,55
Age (médiane)	30 [15-57]	30 [21-51]	0,71
Genre (masculin)	57 (53)	79 (70)	**0,01**
Immunodépression	7	3	0,20
Diabète	5	3	0,48
Durée d'évolution (mois), médiane	4 [3-6]	3 [2-4]	0.008
Nombre de lésions , médiane	2 [1-4]	1,5 [1-3]	
Continent d'acquisition de l'infection			**<0,0001**
Ancien Monde	94	45	
Nouveau Monde	13	68	
Site lésionnel			**0,02**
Membres supérieurs	40	30	
Tête	35	26	
Membres inférieurs	15	38	
Mains	6	7	
Tronc	2	5	
Pieds	5	4	
Cou et cuir chevelu	3	3	
Diamètre (mm), **médiane [IQR]**	19 [10-30]	31 [20-50]	<0,0001
Lymphangite nodulaire	8	32	<0,0001

1. Le taux de guérison est similaire dans les deux groupes
2. Traitements prescrits à des patients atteints de formes différentes
3. Caractéristiques différentes des groupes reflètent plus le respect des recommandations passées (pas de traitement local dans le nouveau monde) que des différences d'applicabilité du traitement local (nbre, taille et topographie des lésions)
4. 12 des 13 patients du Nouveau Monde traités localement ont guéri.

Evaluation et pratique du traitement local

Ben Salah, Buffet et al. PLoS NTD 2009, Ben Salah et al. NEJM 2013
Sosa et al. PLoS NTD 2019

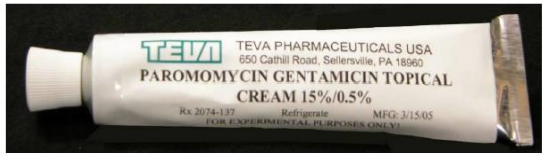
TABLEAU III

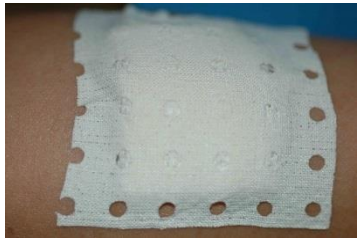
Résultats des essais comparant la cryothérapie, les injections intralésionnelles de dérivés de l'antimoine et la combinaison de ces deux interventions

Référence	N° de patients inclus	Taux de guérison à 6 semaines		
		Antimoine intralésionnel seul	Cryothérapie seule	Cryothérapie + antimoine intralésionnel
El-Darouti1990 Arabie Saoudite	54	44 % (MA)	68 %	100 % (MA)
Asilian 2003 Iran	180	50 % (MA)	Non fait	89,5 % (MA) 92,3 % (SSG)
Asilian 2004 Iran	400	57,43 % (MA)	55,15 %	90,9 % (MA)

MA : Méglumine antimoniate. SSG : Sodium stibogluconate.

Topical Paromomycin + Gentamicin
Third Generation Topical Formulation





Study Design	Institution Location Principal Investigator	Population	Target Enrollment	Parasite species	Start Date	Duration
Phase 3 (A-14134.1)	Institut Pasteur de Tunis Tunisia Dr. Afif Ben Salah	Adults & children (endemic area)	375 *(Actual = 375)*	*L. major*	*January 2008 (completed July 2011)*	*3.5 years*
Phase 2 PK (A-15809)	NMRCD, UPCH Lima, Peru Dr. Alejandro Llanos Cuentas	Adults & children (endemic area)	30 *(Actual = 30)*	*L. peruviana*	*January 2010 (completed March 2011)*	*1 year*
Phase 2 PK (A-15810)	ICGES Panama City, Panama Dr. Nestor Sosa	Adults & children (endemic area)	30 *(Actual = 30)*	*L. panamensis*	*February 2010 (completed March 2011)*	*1 year*
Phase 2 PK (A-16049)	WRNMMC Washington, DC COL Glenn Wortmann	US naive adults (travelers)	30 *(Actual = 1)*	*multiple*	*July 2010 (completed December 2013)*	*3 years*
Phase 2 (Open-label Tx; A-14134.2)	L'Hôpital Pitié Salpêtriére Paris, France Dr. Pierre Buffet	Adults & children (travelers)	30 *(3 enrolled as of 24 June 2014)*	*multiple*	***September 2013 (on-going)***	*2 years*
Phase 2 (Open label Tx; A-16898.3)	Institut Pasteur de Tunis Tunisia Dr. Afif Ben Salah	Adults (endemic area)	120 *(Actual = 50)*	*L. major*	*December 2011 (Study terminated March 2013)*	*1 year*
Expanded Access Tx (M-10337)	DoD MTFs Dr. Naomi Aronson	DoD Healthcare Beneficiaries	Open *(0 enrolled as of 24 June 2014)*	*multiple*	***January 2014 (on-going)***	*3 years*
Phase 3 (A-17540)	ICGES Panama City, Panama Dr. Nestor Sosa	Adults & children (endemic area)	300 *(207 enrolled as of 24 June 2014)*	*multiple*	***May 2013 (on-going)***	*1-2 years*

ORIGINAL ARTICLE

Topical Paromomycin with or without Gentamicin for Cutaneous Leishmaniasis

RESEARCH ARTICLE

Self-application of aminoglycoside-based creams to treat cutaneous leishmaniasis in travelers

Oussama Mouri[1☯], Cléa Melenotte[2☯*], Romain Guéry[3☯], Camille Cotteret[4], Arnaud Schweitzer-Chaput[4], Alice Perignon[5], Marc Thellier[1], Emmanuelle Bourrat[6,7,8], Florentia Kaguelidou[9], Jean Yves Siriez[10], Denis Malvy[11,12], Jean-Pierre Gangneux[13], Alexandre Duvignaud[11,12], Christophe Ravel[14], Salvatore Cisternino[15], Janet Ransom[16], Eric Caumes[17,18], Olivier Lortholary[2,19], Max Grogl[20,21], Pierre Buffet[22]

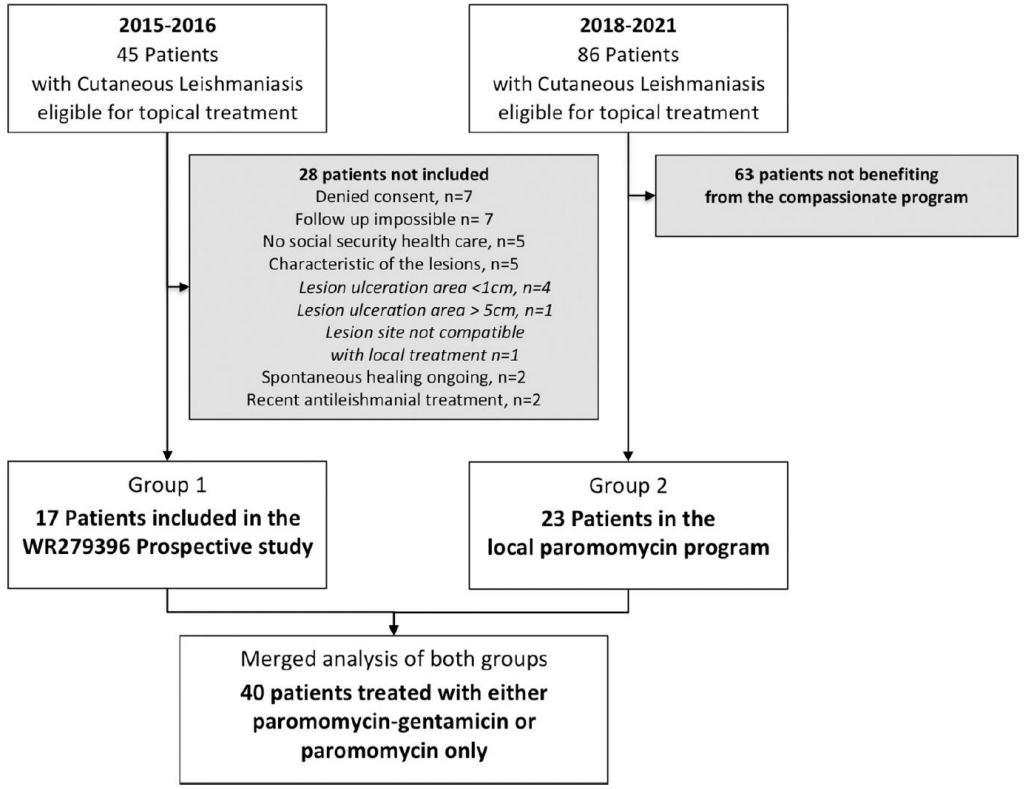


Fig 1. Study flowchart for Group 1 & 2.

https://doi.org/10.1371/journal.pntd.0011492.g001

OPEN ACCESS

Citation: Mouri O, Melenotte C, Guéry R, Cotteret C, Schweitzer-Chaput A, Perignon A, et al. (2023) Self-application of aminoglycoside-based creams to treat cutaneous leishmaniasis in travelers. PLoS Negl Trop Dis 17(8): e0011492. https://doi.org/10.1371/journal.pntd.0011492

Table 1. Baseline demographics and main clinical features.

	Group 1 Prospective study with WR279396	Group 2 Treatment program with local formulation of paromomycin cream
	2015–2016	2018–2021
N	17	23
N (%) female	7/10 (41)	8/23 (35)
Median age (range)	36 (3–68)	29 (5–87)
Mean age (±SD)	35.38 ± 22	36.2±23.7
N (%) children (< 15 yo)	3 [18]	4 [17]
Mean lesion number (N = 164)	2.8 [1]	2.4
Median lesion number (N = 164)	2	2
N (%) patients with > 10 lesions (N = 164)	0	0
Mean lesion number if >10 excluded (N = 157)	2.8	2.3
Median lesion duration (months) (N = 82)	3.5	3.5
N (%) ulcerative lesions (N = 167)	17 (100) [2]	17 (73)
Median ulceration area (mm2)(N = 132)	265	165
N (%) patients infected in the New World (N = 166)	6 (35)	8 [34]

Cutaneous Leishmaniasis

PLOS NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Self-application of aminoglycoside-based creams to treat cutaneous leishmaniasis in travelers

Oussama Mouri[1☯], Cléa Melenotte[2☯*], Romain Guéry[3☯], Camille Cotteret[4], Arnaud Schweitzer-Chaput[4], Alice Perignon[5], Marc Thellier[1], Emmanuelle Bourrat[6,7,8], Florentia Kaguelidou[9], Jean Yves Siriez[10], Denis Malvy[11,12], Jean-Pierre Gangneux[13], Alexandre Duvignaud[11,12], Christophe Ravel[14], Salvatore Cisternino[15], Janet Ransom[16], Eric Caumes[17,18], Olivier Lortholary[2,19], Max Grogl[20,21], Pierre Buffet[22]

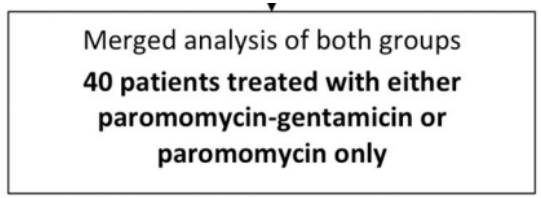
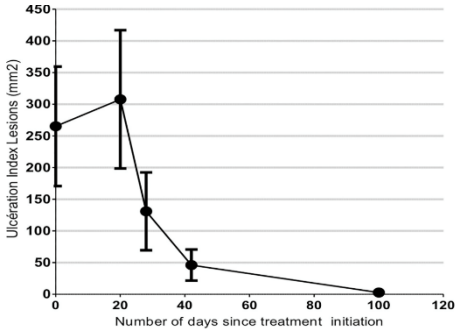


Fig 1. Study flowchart for Group 1 & 2.



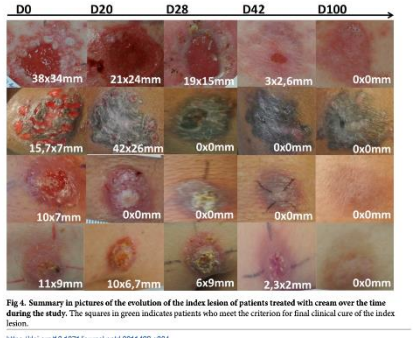
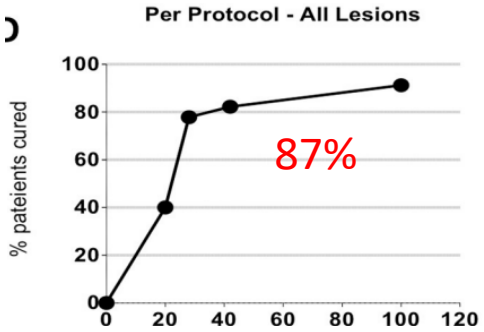
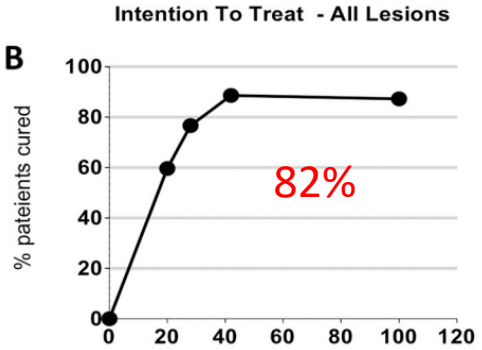


Fig 4. Summary in pictures of the evolution of the index lesion of patients treated with cream over the time during the study. The squares in green indicates patients who meet the criterion for final clinical cure of the index lesion.





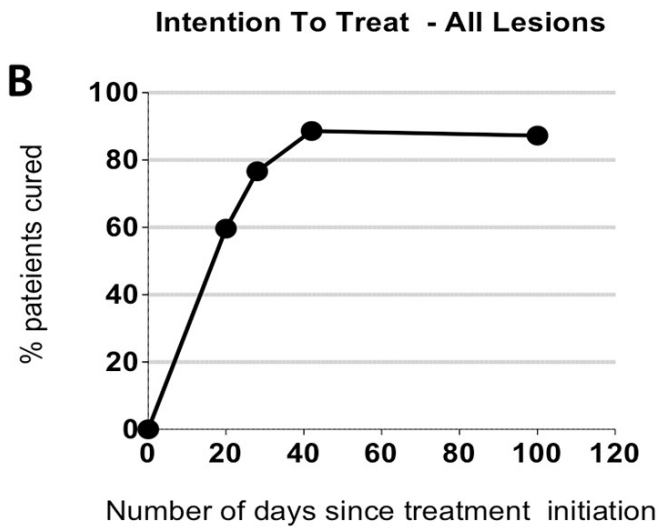
There was a trend towards better therapeutic outcomes against Old World CL than New World (83.3% v. 60%, p=0.14)

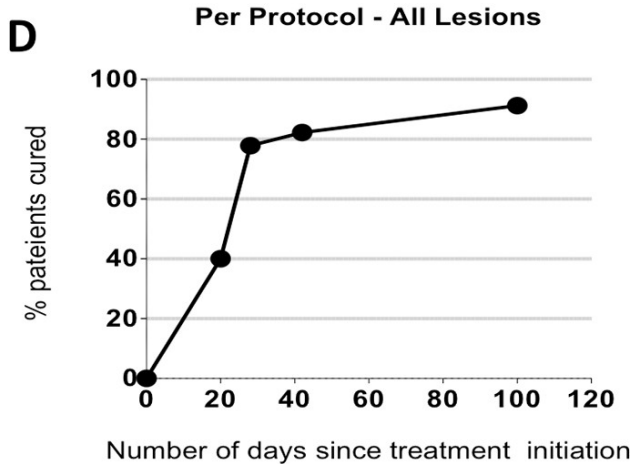
No mucosal involvement was observed in either group.

Advantages : painless, self-applicable, low cost

Inconvenients: not available, no standardized product

Mouri* Melenotte*, *Plos NTD, 2023*





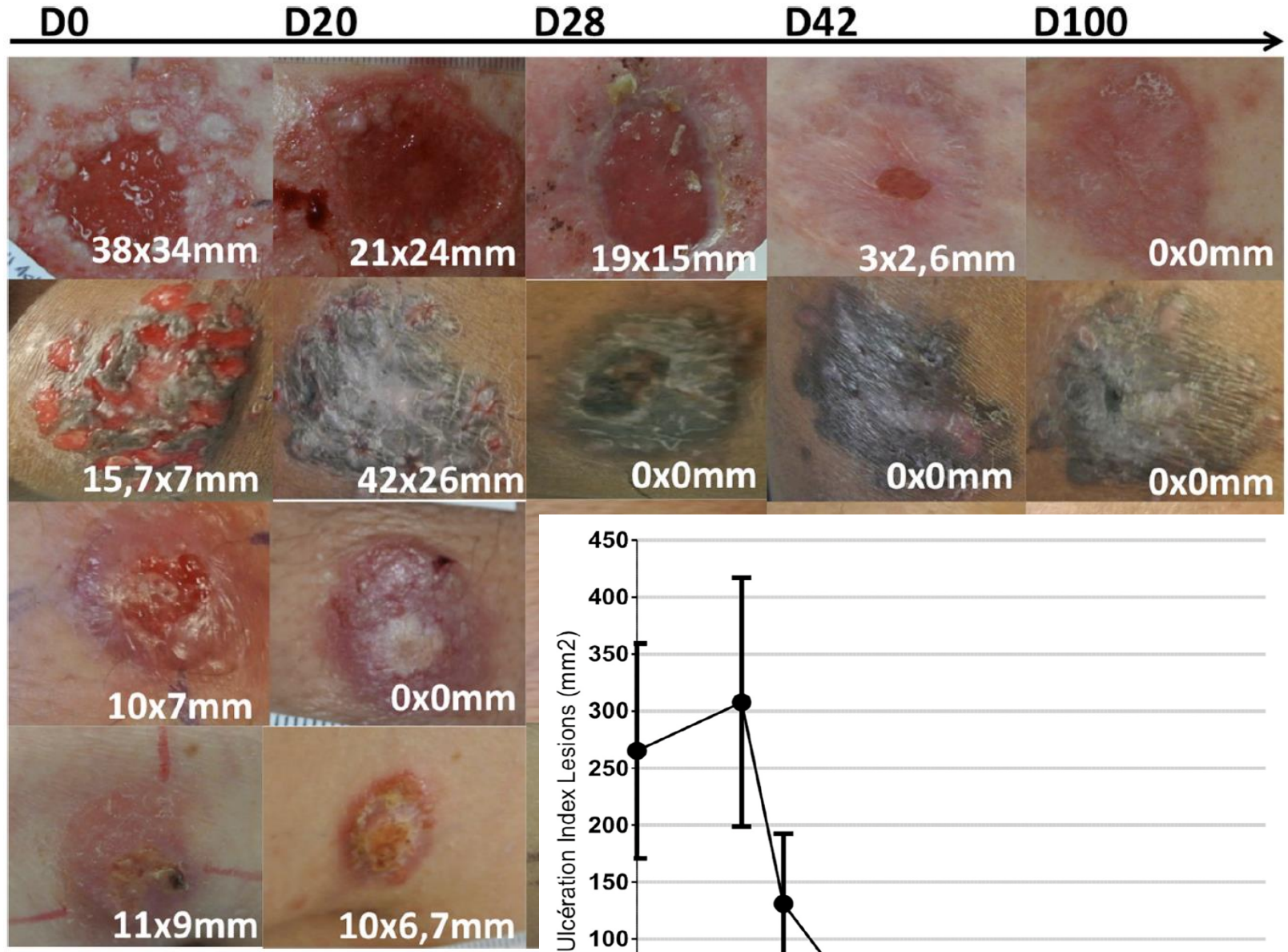
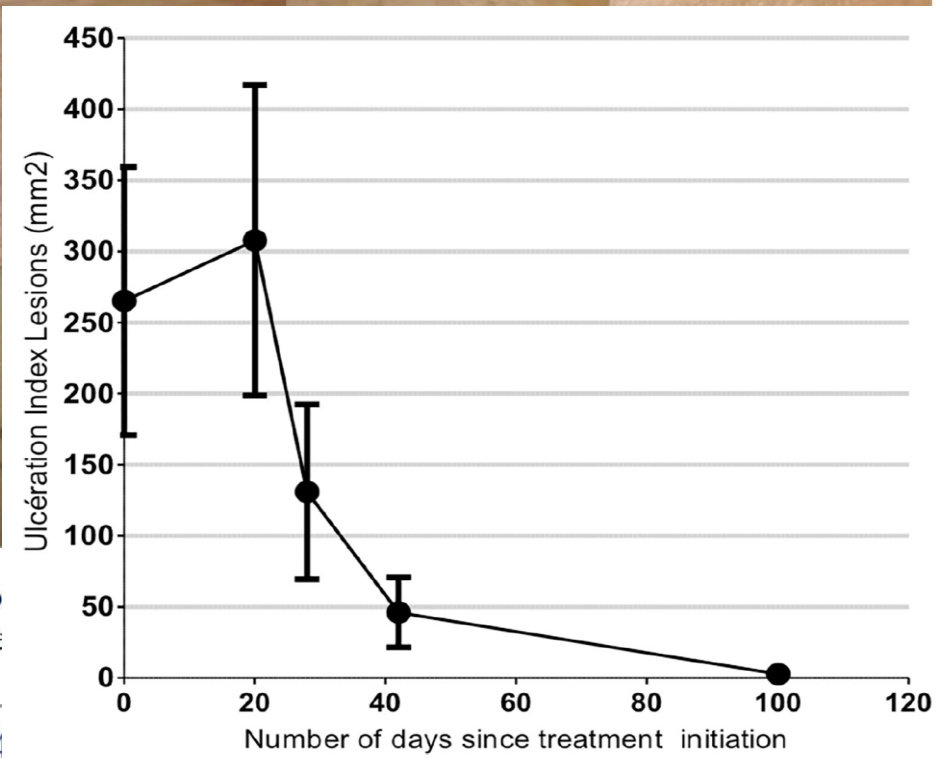
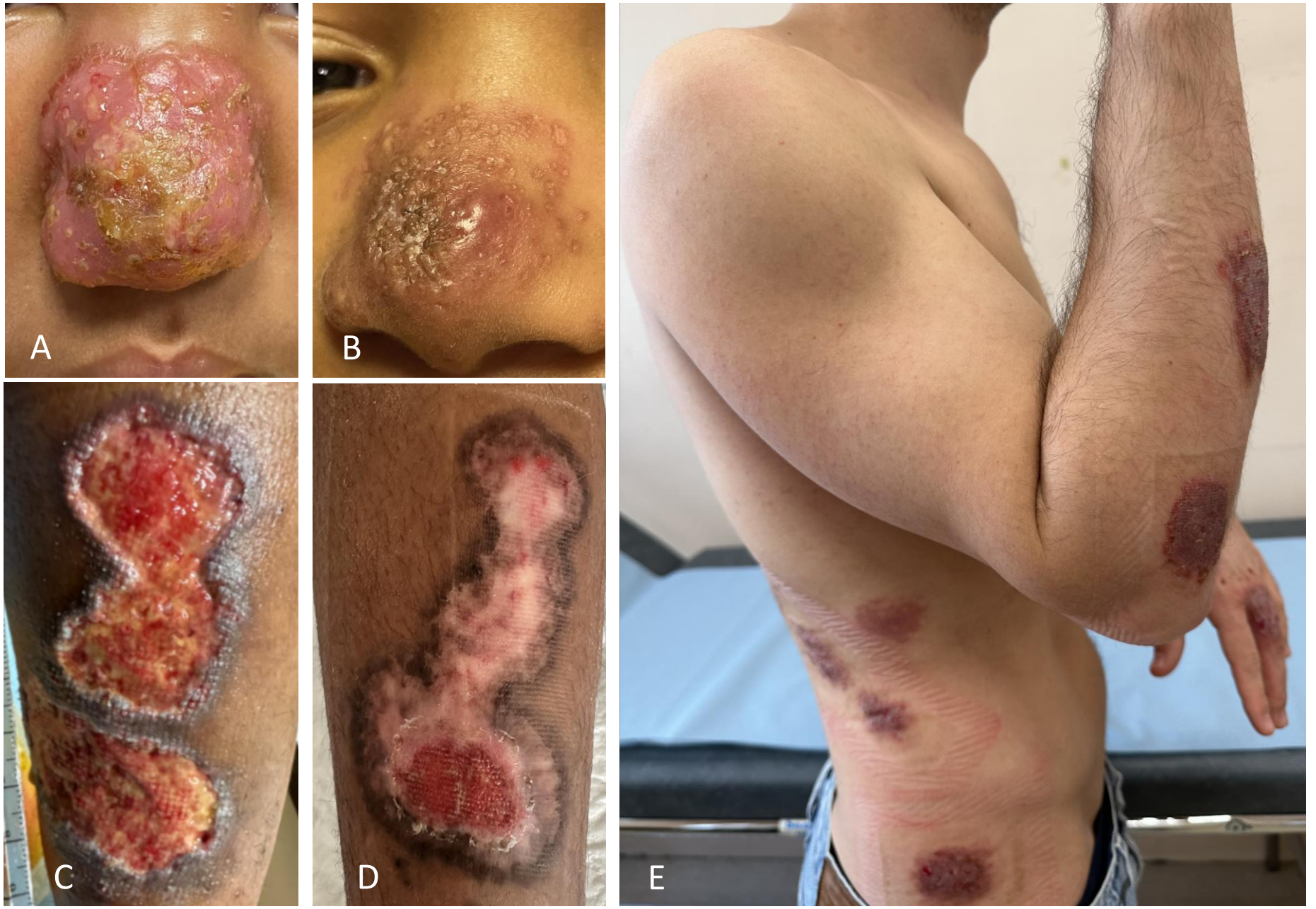


Fig 4. Summary in pictures of the evolution o during the study. The squares in green indicate lesion.

https://doi.org/10.1371/journal.pntd.0011492.g004



Would you prefer injections or burns?



DNDi portfolio

Leishmaniasis	Screening			DNDI-6174	DNDI-6148	LXE408 Novartis for VL	Miltefosine + thermo-therapy for CL	Miltefosine + paromomycin for VL (Africa)	SSG + PM (East Africa)*
				DNDI-8526 (S07 series)	DNDI-0690		LAmB +/- miltefosine for PKDL (Asia)	Miltefosine + paromomycin or LAmB for PKDL (Sudan)	New VL treatments (South Asia)*
					DNDI-6899 (GSK899 DDD853651)				New treatments for VL/HIV*
					CpG-D35 (DNDI-2319)				New VL treatments (Latin America)*
					GSK245 (DDD1305143)				

Oral drug

Oral drugs

Useful for CL?

Au total

1. Ancien monde: tous sauf *L. infantum* et immunodépression

   Paromomycine locale dès que possible

   sinon cryothérapie + intralésionnelles de glucantime

   Cas complexe: Miltéfosine 2 - 2,5 mg/kg/j x 28j (Attention risque tératogène+++)

2. Ancien monde: *L. infantum* et immunodépression

   AmBisome > 30 mg/kg cumulés

3. Nouveau Monde Guyane

Pentamidine 4 mg/kg x 3 ou AmBisome ou traitement local (Consult ORL Accord patient Certificat)

4. Nouveau Monde autre

   Glucantime 20 mg Sb5/kg/j x 20 j ou traitement local (Consult ORL Accord patient Certificat)

5. Toute situation complexe

   Miltéfosine orale 2 - 2,5 mg/kg/j x 28j

Ordonnance type et certificat

1. Paromomycine crème : 1 application locale 1 fois par jour pendant 30 jours
   Après avoir nettoyé la peau à 'eau et au savon, bien rincer et bien sécher sans frotter, appliquer la crème sur la partie ouverte (« ulcérée ») des lésions en veillant à ne pas en mettre sur la peau saine autour de la/des lésions. Bien mélanger la crème dans le pot avant chaque application pour qu'elle soit bien homogène. Conserver de préférence le pot au réfrigérateur.

2. Appliquer ensuite le pansement URGOTULLE LITE Pans hydrocelllulaire 6,5x10 cm B/10 en le collant bien sur la peau saine autour de la/des lésions. Laisser le pansement jusqu'à l'application suivante, ou au moins 12 heures.

3. En cas d'irritation et/ou de démangeaisons persistantes sur les bords de la/des lésions appliquer une fois par jours la crème désonide 0,05% (TRIDESONIT 0,05% CR TB 30 G) sur les zones irritées, sans appliquer sur la partie ouverte de la/des lésions.

4. Se laver les mains après application

Pharmacien à contacter : arnaud.schweitzer-chaput@aphp.fr

Merci d'assurer un suivi rigoureux à J20, J30, J60 et J90 (à partir du début du traitement) et de nous informer de l'évolution idéalement avec photo.

Contacts :

Cléa Melenotte clea.melenotte@aphp.fr

Pierre Buffet pierre.buffet@pasteur.fr

Je soussigné Dr.

certifie avoir pris en charge M/Me

Pour une leishmaniose cutanée due à Leishmania

Confirmée par Frottis Culture PCR Autre

Traitée par pendant jours

Cicatrisation complète constatée le

Compte tenu d'un risque faible mais non nul de leishmaniose muqueuse secondaire pouvant survenir quelques semaines à plusieurs décennies après cet épisode, je recommande une consultation en cas de symptômes ORL inhabituels (obstruction nasale, lésions du nez, de la bouche, ou ailleurs dans la zone ORL) durant plus de 2 semaines, de consulter un spécialiste ORL et/ou Infectiologue et/ou dermatologue avec ce certificat pour confirmation diagnostique et traitement.

Fait à le

Leishmaniose Points clés

Viscérale

1. Maladie surtout européenne
2. PCR sang quantitative d'abord
3. **AmBisome 21 mg/kg cumulés**
4. Immunodéprimé 40-60 mg/kg cumulés et contrôler la charge (PCR négative) avant prophylaxie 2aire par AmBisome ou miltéfosine ou pentamidine ou antimoine ou paromomycine

L'Amphotéricine B liposomale
est formidable mais ne résout pas tout

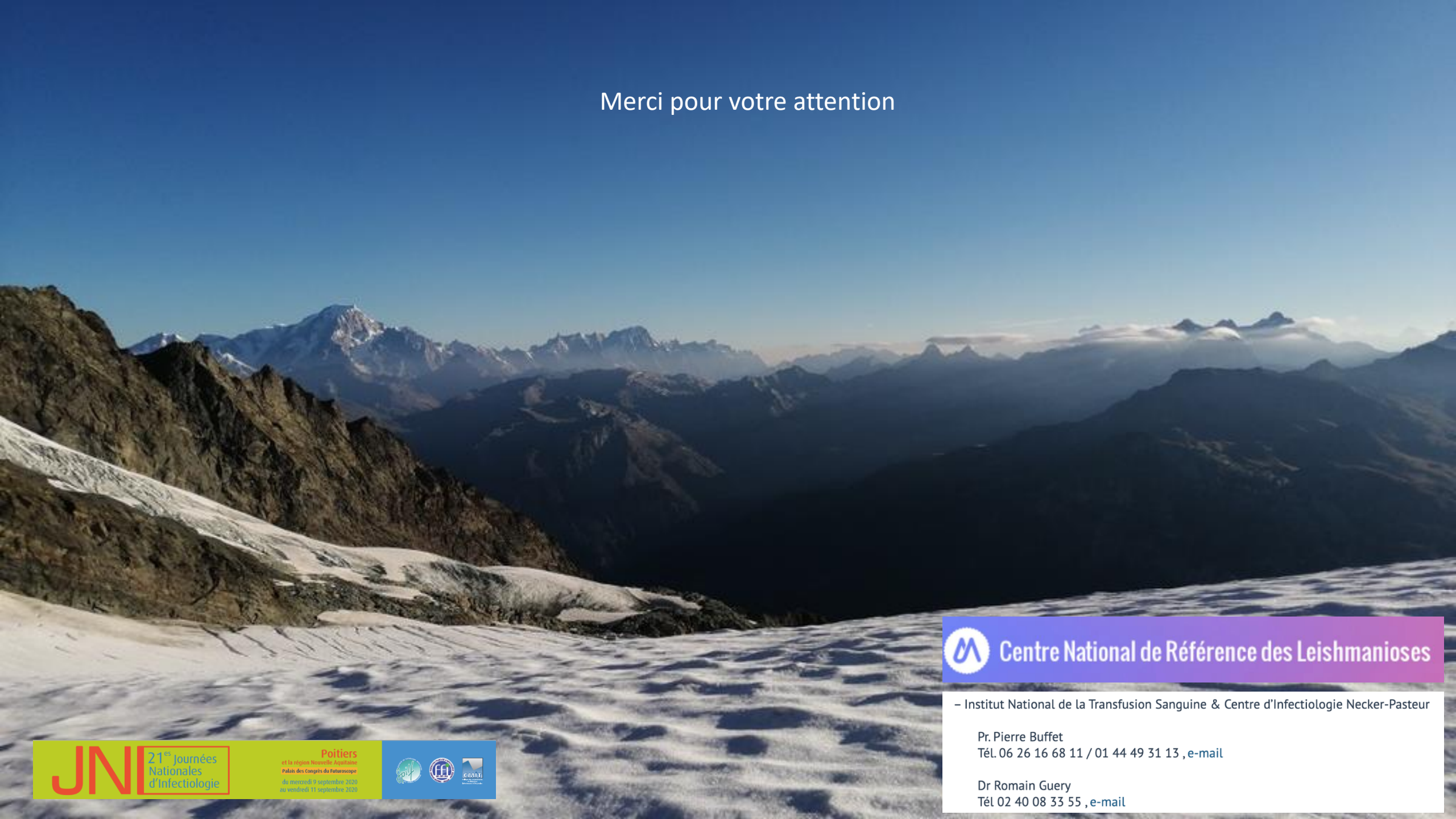
Cutanée

1. **Lésion infiltrée prolongée inexpliquée au retour**
2. Qualité du prélèvement local
3. Bénéfice-risque difficile à déterminer car maladie rarement grave
4. Traitement local svt possible (crème paromomycine ou CryoSbIL*)
5. Association *L. infantum*
Immunodépression Atteinte muqueuse
AmBisome > 30 mg/kg cumulés

*CryoSbIL
= Cryothérapie et injections intra-lésionnelles de Glucantime

N'hésitez pas à appeler ou écrire : 06 26 16 68 11 pierre.buffet@pasteur.fr clea.melenotte@aphp.fr

Merci pour votre attention



Centre National de Référence des Leishmanioses

– Institut National de la Transfusion Sanguine & Centre d'Infectiologie Necker-Pasteur

Pr. Pierre Buffet
Tél. 06 26 16 68 11 / 01 44 49 31 13 , e-mail

Dr Romain Guery
Tél 02 40 08 33 55 , e-mail

JNI 21es Journées Nationales d'Infectiologie
Poitiers
et la région Nouvelle Aquitaine
Palais des Congrès du Futuroscope
du mercredi 9 septembre 2020
au vendredi 11 septembre 2020

Cas cliniques

1

♂

40-year old
Born in France Living in France
No preexisting condition
Visited Sidi-Bouzid (central Tunisia) in July
This single lesion appeared in August
Smear and aspirate positive for *Leishmania* in October
Physical examination normal.
Does not like injections
Would withstand the inconvenience for a few more months

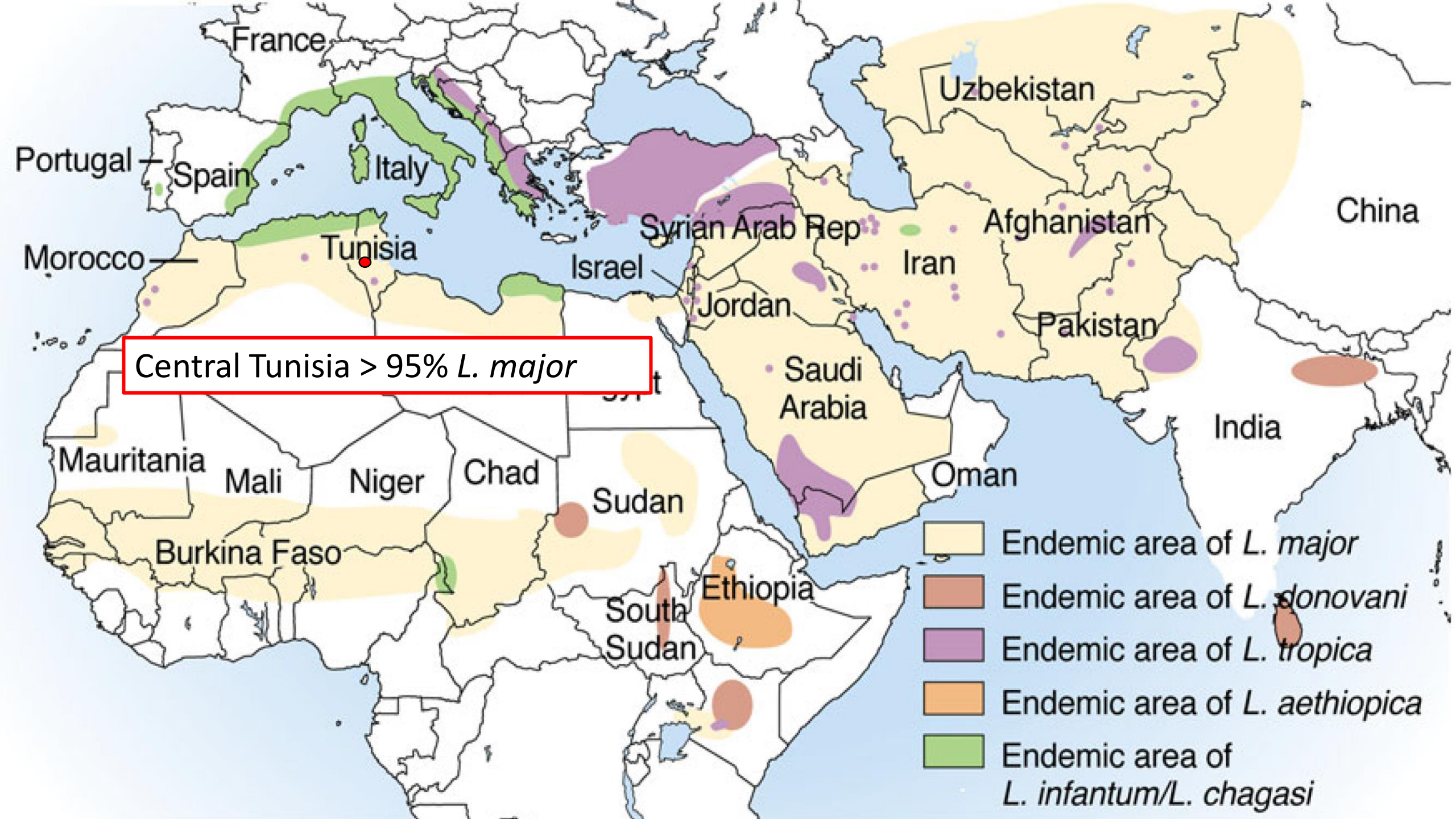
Gestion sans traitement spécifique

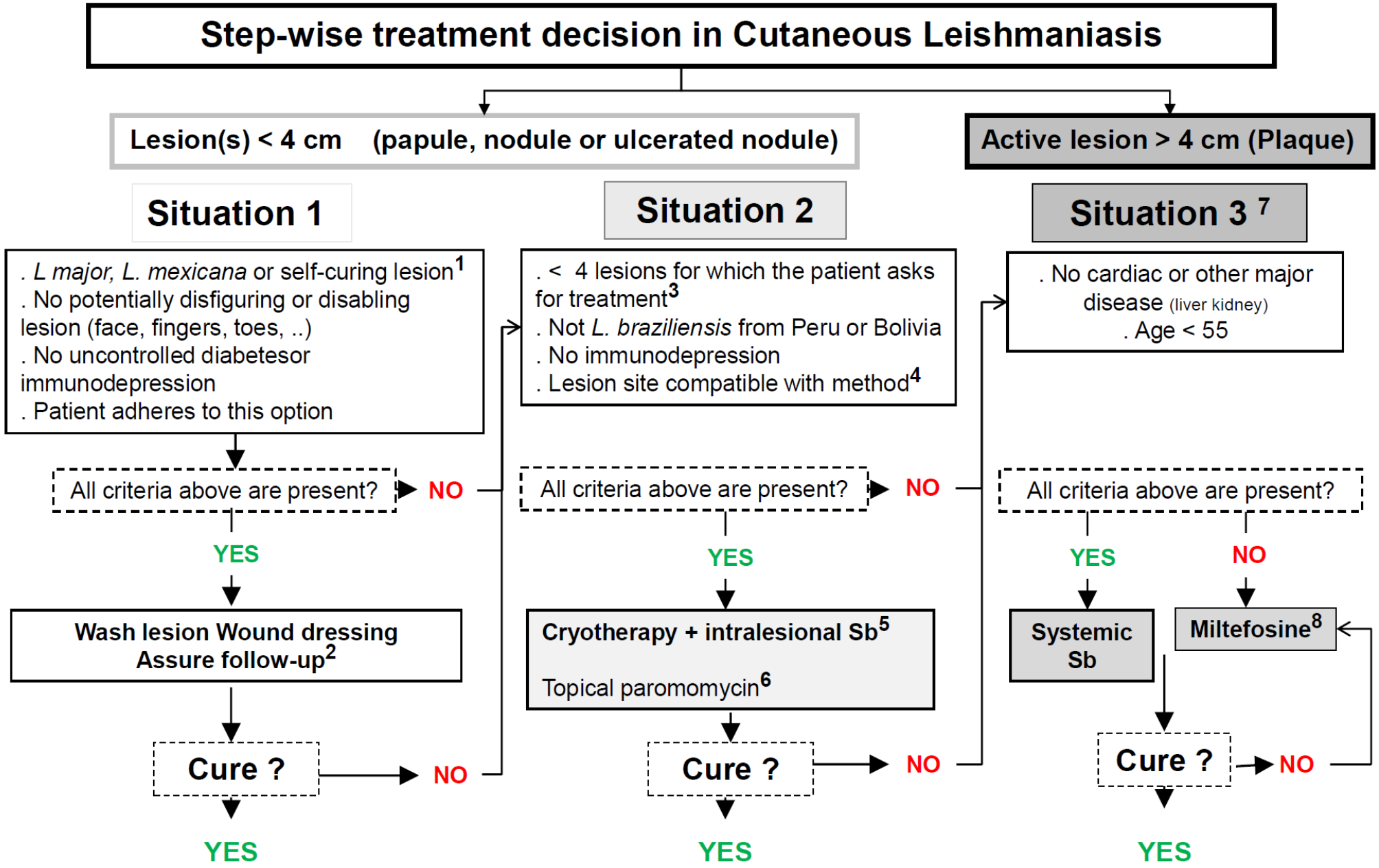
Aucun risque de VL ou de ML (Internet n'est pas fiable)
Pas de risque de transmission dans la famille (pas de phlébotomes)
Aucun traitement indolore disponible

- 75% de guérison en 3 mois mais revenez quand vous voulez et nous ferons quelque chose

Information du patient

- <u>Revient à 2 mois sans amélioration</u> <u>Demande de traitement</u>


France
Portugal
Spain
Italy
Morocco
Tunisia
Israel
Syrian Arab Rep
Uzbekistan
Afghanistan
China
Iran
Jordan
Pakistan
Saudi Arabia
India
Oman
Mauritania
Mali
Niger
Chad
Sudan
Burkina Faso
Ethiopia
South Sudan
Central Tunisia > 95% L. major
Endemic area of L. major
Endemic area of L. donovani
Endemic area of L. tropica
Endemic area of L. aethiopica
Endemic area of
L. infantum/L. chagasi


Step-wise treatment decision in Cutaneous Leishmaniasis
Lesion(s) < 4 cm (papule, nodule or ulcerated nodule)
Active lesion > 4 cm (Plaque)
Situation 1
Situation 2
Situation 3 7
. L major, L. mexicana or self-curing lesion1
. No potentially disfiguring or disabling lesion (face, fingers, toes, ..)
. No uncontrolled diabetesor immunodepression
. Patient adheres to this option
. < 4 lesions for which the patient asks for treatment3
. Not L. braziliensis from Peru or Bolivia
. No immunodepression
. Lesion site compatible with method4
. No cardiac or other major disease (liver kidney)
. Age < 55
All criteria above are present?
NO
YES
Wash lesion Wound dressing
Assure follow-up2
Cryotherapy + intralesional Sb5
Topical paromomycin6
Systemic Sb
Miltefosine8
Cure ?

4

♂

56-year old
Born in France Living in France Small aircraft pilot
Arterial hypertension and supraventricular arrythmia.
Sclerosis cholangitis without impairment of liver function
Went to South Morocco (several places) during summer.
Diagnosis 8 months later (Biopsy positive for *Leishmania).*
12 lésions all infiltrated and 2 (on the leg) are still ulcerated despite treatment with fluconazole (200 mg/d x 6 weeks), liposomal amphotericin B (20 mg/kg total dose) and Glucantime (6 mg Sbv/kg/d 1 ampule/d x 35 days without lab or EKG follow-up) ongoing.
Physical examination normal. Species identification is *L. major*
Worried that the infection could go visceral or mucosal. Very angry with medical team.
Do you need more information?

How will you treat ?

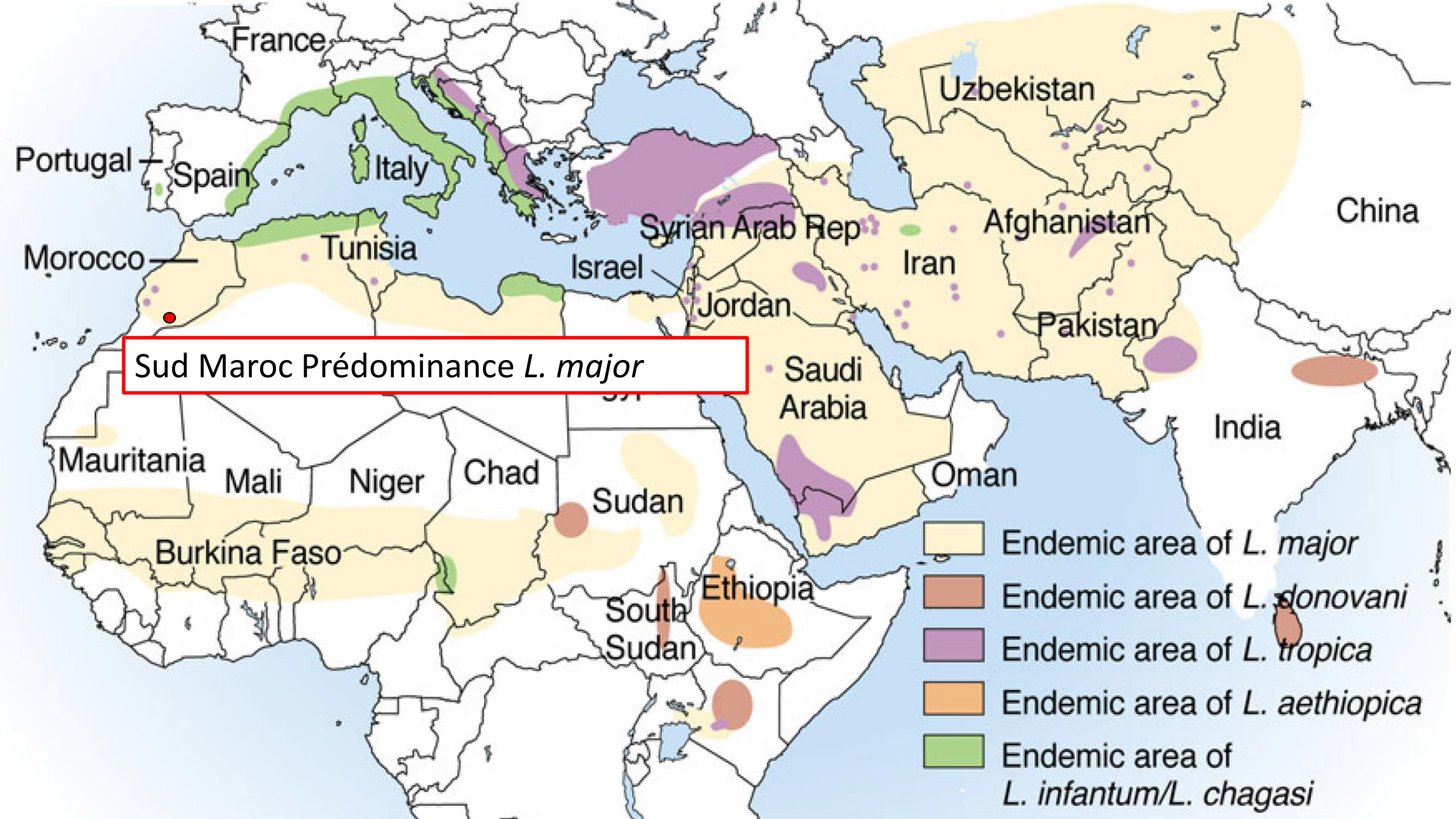

France
Portugal
Spain
Italy
Morocco
Tunisia
Israel
Syrian Arab Rep
Jordan
Uzbekistan
Afghanistan
Iran
China
Pakistan
Saudi Arabia
India
Oman
Mauritania
Mali
Niger
Chad
Sudan
Burkina Faso
Ethiopia
South Sudan
Sud Maroc Prédominance L. major
Endemic area of L. major
Endemic area of L. donovani
Endemic area of L. tropica
Endemic area of L. aethiopica
Endemic area of
L. infantum/L. chagasi

Table 1. Main characteristics of 43 patients with tegumentary leishmaniasis treated with liposomal amphotericin B.

Characteristics of patients		n = 43
Demographics		
	Median age, years [range]	51 [1–86]
	Male	29 (67)
	Cardiovascular comorbidities and/or diabetes	7 (16)
	Immunocompromised subject	5 (12)
	Child	6 (14)
Clinical form		
	Localized cutaneous	32 (74)
	Mucocutaneous	8 (19)
	Disseminated cutaneous	2 (5)
	Localized cutaneous with visceral involvement	1 (2)
Area where infection was acquired		
	Old World	28 (65)
	New World	15 (35)
***Leishmania* Species (n = 35; 8 species unidentified)**		
	L. braziliensis	11 (31)
	L. braziliensis complex	2 (6)
	L. guyanensis	1 (3)
	L. amazonensis	1 (3)
	L. infantum	9 (26)
	L. major	6 (17)
	L. tropica	3 (8)
	L. donovani	2 (6)
Clinical findings		
	Number of lesions, median [range]	2 [1–30]
	Larger lesion size (millimeter), median [range]	30 [4–200]
Treatment		
	Frontline therapy with L-AmB	30 (70)
	Liposomal AmB cumulative dose (mg/kg), median [range]	20 [6–56]
	Number of infusions, median [range][a]	6 [2–14]
Outcome		
	Follow-up (days), median [range]	79 [28–803]
	Complete healing without relapse	19 (44)
	Improvement	2 (5)
	Failure	17 (39)
	Relapse	5 (12)
Adverse events		
	Patients with at least one adverse event	23 (53)
	Treatment modification due to adverse events	7 (16)

PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Liposomal amphotericin B in travelers with cutaneous and muco-cutaneous leishmaniasis: Not a panacea

Romain Guery[1☯*], Benoit Henry[1☯], Guillaume Martin-Blondel[2], Claire Rouzaud[1], Florence Cordoliani[3], Gundel Harms[4], Jean-Pierre Gangneux[5], Françoise Foulet[6], Emmanuelle Bourrat[7], Michel Baccard[3], Gloria Morizot[8], Paul-Henri Consigny[9], Antoine Berry[10], Johannes Blum[11], Olivier Lortholary[1], Pierre Buffet[12☯*], the French Cutaneous Leishmaniasis Study group & the LeishMan network[¶]

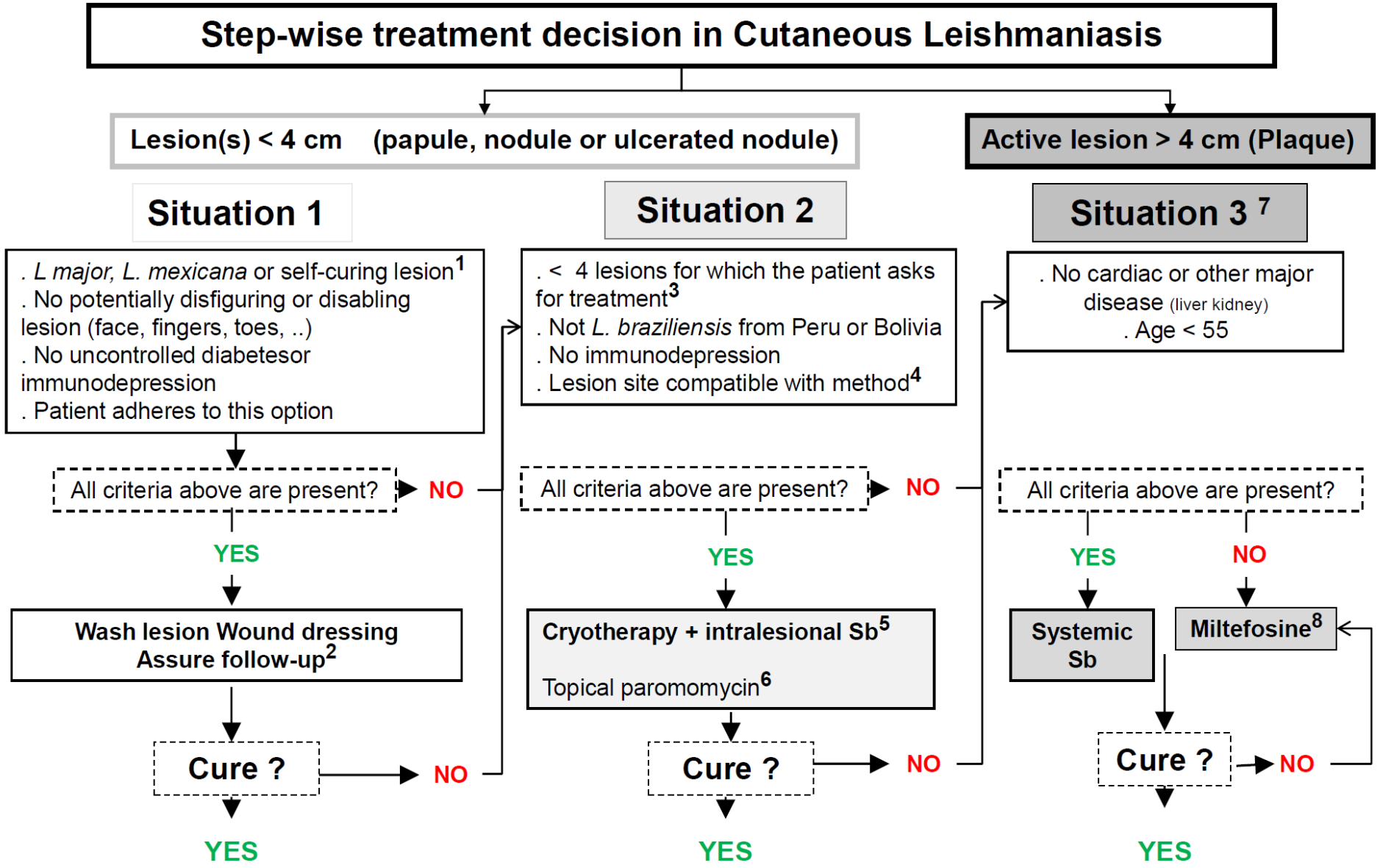
Taux de succès global: 49-63%
Incidence d'effets indésirables 53% dont hypokaliémie

Table 2. Predictors of success of liposomal amphotericin B in 41 patients with tegumentary leishmaniasis.

		Complete healing without relapse	Failure or relapse	Success of L-AmB	p value
		n = 19[a]	n = 22[a]	(%)	
Patients					
Age		57 [2–80]	42 [1–86]	/	0.58
Immunocompromised subject		2 (10)	3 (14)	40	0.99
Localized cutaneous form		14 (74)	17 (77)	45	0.99
Mucocutaneous form		4 (21)	3 (14)	57	0.68
Frontline therapy with L-AmB		15 (79)	15 (68)	50	0.44
Country where infection was acquired					
Old World		15 (79)	11 (50)	58	0.05
New World		4 (21)	11 (50)	27	0.05
Leishmania species					
Viannia subgenus		4 (21)	10 (45)	28	0.13
L. infantum		7 (37)	2 (9)	78	0.06
L. major		2 (10)	4 (18)	50	0.99
Clinical findings					
Number of lesions		2 [1–30]	2 [1–8]	/	0.84
Treatment					
Cumulative dose of L-AmB (mg/kg)		20 [6–40]	20 [16–56]	/	0.73

L-AmB, liposomal amphotericin B. Data are represented as n (%) or median [range] unless otherwise indicated.

[a]Two patients with improvement at first control visit (before day 90) but no subsequent follow-up were excluded from the analysis.



Décision: Les lésions étaient vraiment trop grandes et nombreuses pour paromomycine locale (ce qui est rare)
Traitement par miltéfosine qui a été dans ce cas bien toléré et efficace